09/ 960,477

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NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 4	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 5	FEB 05	German (DE) application and patent publication number format changes
NEWS 6	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS 7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS 8	MAR 03	FRANCEPAT now available on STN
NEWS 9	MAR 29	Pharmaceutical Substances (PS) now available on STN
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NEWS 11	MAR 29	No connect hour charges in WPIFV until May 1, 2004
NEWS 12	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 11:20:49 ON 13 APR 2004

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 11:21:02 ON 13 APR 2004

09/ 960,477

FILE LAST UPDATED: 10 APR 2004 (20040410/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> e cholinesterase
E1            4     CHOLINESTERAS/BI
E2            7     CHOLINESTERASA/BI
E3        18588 --> CHOLINESTERASE/BI
E4            1     CHOLINESTERASE2/BI
E5            1     CHOLINESTERASEACTIVITAS/BI
E6            1     CHOLINESTERASEAKTIVITAET/BI
E7            1     CHOLINESTERASEAKTIVITASA/BI
E8            1     CHOLINESTERASEAKTIVITASANAK/BI
E9           23     CHOLINESTERASEAKTIVITAT/BI
E10           2     CHOLINESTERASEAKTIVITATEN/BI
E11           1     CHOLINESTERASEAKTTVITAT/BI
E12           1     CHOLINESTERASEANTAGONISTEN/BI

=> s e1-e3
              4 CHOLINESTERAS/BI
              7 CHOLINESTERASA/BI
          18588 CHOLINESTERASE/BI
L1        18590 (CHOLINESTERAS/BI OR CHOLINESTERASA/BI OR CHOLINESTERASE/BI)

=> e urinary
E1            2     URINARUM/BI
E2            2     URINARV/BI
E3       200023 --> URINARY/BI
E4            1     URINARYAD7C/BI
E5            1     URINARYEXCRETION/BI
E6            1     URINARYL/BI
E7            1     URINARYNI/BI
E8            1     URINARYS/BI
E9            1     URINARYTOXICITY/BI
E10           2     URINARYTRACT/BI
E11           1     URINARYU/BI
E12           1     URINARYVOLUME/BI

=> s e2 or e3 or e5 or e12
              2 URINARV/BI
         200023 URINARY/BI
              1 URINARYEXCRETION/BI
              1 URINARYVOLUME/BI
L2       200026 URINARV/BI OR URINARY/BI OR URINARYEXCRETION/BI OR URINARYVOLUME
                /BI

=> s l1 and l2
L3          172 L1 AND L2

=> e muscarinic
E1            4     MUSCARINES/BI
E2            2     MUSCARINI/BI
E3        21667 --> MUSCARINIC/BI
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09/ 960,477

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E4            8      MUSCARINIC1/BI
E5            3      MUSCARINIC2/BI
E6            1      MUSCARINIC4/BI
E7            2      MUSCARINICA/BI
E8           20      MUSCARINICALLY/BI
E9            1      MUSCARINICE/BI
E10           3      MUSCARINICI/BI
E11           3      MUSCARINICO/BI
E12           8      MUSCARINICOS/BI

=> s e3-e6
          21667 MUSCARINIC/BI
              8 MUSCARINIC1/BI
              3 MUSCARINIC2/BI
              1 MUSCARINIC4/BI
L4        21668 (MUSCARINIC/BI OR MUSCARINIC1/BI OR MUSCARINIC2/BI OR MUSCARINIC
                4/BI)

=> s l1 and l2 and l4
L5           13 L1 AND L2 AND L4

=> s (l1 or l4) and l2
L6          712 (L1 OR L4) AND L2

=> s l6 and (dysuria or (urinary bladder))
           1700 DYSURIA
         200023 URINARY
          93807 BLADDER
          14036 URINARY BLADDER
                  (URINARY(W)BLADDER)
L7          327 L6 AND (DYSURIA OR (URINARY BLADDER))

=> s l7 and inhibit?
        1095051 INHIBIT?
L8          154 L7 AND INHIBIT?

=> s (l1 or l4) and inhibit?
        1095051 INHIBIT?
L9        21065 (L1 OR L4) AND INHIBIT?

=> s l9 and l2
L10         298 L9 AND L2

=> s l10 and (dysuria or bladder?)
           1700 DYSURIA
          94128 BLADDER?
L11         198 L10 AND (DYSURIA OR BLADDER?)

=> s l11 not py>1998
        2690081 PY>1998
L12         121 L11 NOT PY>1998

=> d l12 1- ibib abs
YOU HAVE REQUESTED DATA FROM 121 ANSWERS - CONTINUE? Y/(N):y
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L12 ANSWER 1 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1999032785 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9791087
TITLE: M2 **muscarinic** receptor contributes to contraction of the denervated rat **urinary bladder**.
AUTHOR: Braverman A S; Luthin G R; Ruggieri M R
CORPORATE SOURCE: Department of Urology, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.
CONTRACT NUMBER: RO1-DK-39086 (NIDDK)
RO1-DK-43333 (NIDDK)
SOURCE: American journal of physiology, (1998 Nov) 275 (5 Pt 2) R1654-60.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981210

AB In vitro **bladder** contractions in response to cumulative carbachol doses were measured in the presence of selective **muscarinic** antagonists from rats that had their major pelvic ganglion bilaterally removed. Denervation induced both hypertrophy and a supersensitivity of the **bladders** to agonist. The affinities in control **bladders** for antagonism of carbachol-induced contractions were consistent with M3-mediated contractions. Affinities in denervated **bladders** for 4-diphenlacetoxy-N methylpiperidine methiodide (8.5) and p-fluoro hexahydrosilodifenidol (6.6) were consistent with M2-mediated contractions, although the methoctramine affinity (6.5) was consistent with M3-mediated contractions. Subtype-selective immunoprecipitation of **muscarinic** receptors revealed a 50% increase in total and a 60% increase in M2 receptor density with no change in M3 receptor density in denervated **bladders** compared with normal or sham-operated controls. This increase in M2 receptor density is consistent with the change in affinity of the antagonists for **inhibition** of carbachol-induced contractions and may indicate that M2 receptors or a combination of M2 and M3 receptors directly mediates smooth muscle contraction in the denervated **bladder**.

L12 ANSWER 2 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998420502 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9748713
TITLE: Comparison of the effects of various spasmolytic drugs on isolated human and porcine detrusor smooth muscle.
AUTHOR: Uckert S; Stief C G; Odenthal K P; Becker A J; Truss M C; Jonas U
CORPORATE SOURCE: Hannover Medical School, Department of Urology, Germany.
SOURCE: Arzneimittel-Forschung, (1998 Aug) 48 (8) 836-9.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981109

AB The spasmolytic activity of flavoxate (CAS 15301-69-6), anticholinergic agents oxybutynin (CAS 5633-20-5), and trospium chloride (CAS 10405-02-4), drugs commonly utilized in the therapy of hyperactive **bladder**, and phosphodiesterase (PDE) **inhibitors** papaverine (CAS 58-74-2) and vinpocetine (CAS 42971-09-5) on **muscarinic** contractions of detrusor smooth muscle strips isolated from human and porcine **urinary bladder** was studied in vitro using the organ bath technique. Trospium chloride was most effective in relaxing contractions elicited by **muscarinic** stimulation, while flavoxate was significantly less effective than all other drugs tested. The relaxing potency of oxybutynin was greater than those of PDE-**inhibitors** papaverine and vinpocetine but 3,000 fold less significant than those of trospium chloride. The effects of the individual drugs on **muscarinic** tension of both human and porcine detrusor muscle strips were nearly equal. The present results suggest that the pig might be an appropriate animal model for the study of effects of spasmolytic substances on the contractility of **urinary bladder** smooth muscle in vitro.

L12 ANSWER 3 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998405233 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9734316
TITLE: Selective **muscarinic** antagonists. II. Synthesis and antimuscarinic properties of biphenylylcarbamate derivatives.
AUTHOR: Naito R; Takeuchi M; Morihira K; Hayakawa M; Ikeda K; Shibanuma T; Isomura Y
CORPORATE SOURCE: Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Ibaraki, Japan.
SOURCE: Chemical & pharmaceutical bulletin, (1998 Aug) 46 (8) 1286-94.
Journal code: 0377775. ISSN: 0009 2363.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981002

AB A novel series of biphenylylcarbamate derivatives were synthesized and evaluated for binding to M1, M2 and M3 receptors and for antimuscarinic activities. Receptor binding assays indicated that biphenyl-2-ylcarbamate derivatives had high affinities for M1 and M3 receptors and good selectivities for M3 receptor over M2 receptor, indicating that the biphenyl-2-yl group is a novel hydrophobic replacement for the benzhydryl group in the **muscarinic** antagonist field. In this series, quinuclidin-4-yl biphenyl-2-ylcarbamate monohydrochloride (8l, YM-46303) exhibited the highest affinities for M1 and M3 receptors, and selectivity for M3 over M2 receptor. Compared to oxybutynin, YM-46303 showed approximately ten times higher **inhibitory** activity on **bladder** pressure in reflexly-evoked rhythmic contraction, and about 5 fold greater selectivity for **urinary bladder** contraction against salivary secretion in rats. Moreover, selective antagonistic activity was also observed in vitro. Further evaluation of antimuscarinic effects on bradycardia and pressor in pithed rats, and on tremor in mice, showed that YM-46303 can be useful for the treatment of **urinary** urge incontinence as a **bladder**-selective M3 antagonist with potent activities and fewer side effects.

L12 ANSWER 4 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998405232 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9734315
TITLE: Selective **muscarinic** antagonists. I. Synthesis and antimuscarinic properties of 4-piperidyl benzhydrylcarbamate derivatives.
AUTHOR: Naito R; Takeuchi M; Morihira K; Hayakawa M; Ikeda K; Shibanuma T; Isomura Y
CORPORATE SOURCE: Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Ibaraki, Japan.
SOURCE: Chemical & pharmaceutical bulletin, (1998 Aug) 46 (8) 1274-85.
Journal code: 0377775. ISSN: 0009-2363.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981002

AB A series of 1-substituted-4-piperidyl benzhydrylcarbamate derivatives were synthesized and evaluated for binding affinity to M1, M2 and M3 receptors, and for antimuscarinic activities. Receptor binding assays indicated that 1-benzyl-4-piperidyl benzhydrylcarbamate derivatives showed higher affinities for M1 and M3 receptors, and good selectivities for M3 over M2 receptor, than the corresponding ester analog. These results indicate that the urethane bond is a novel linker for **muscarinic** antagonists, and serves to lock the molecular conformation and allows the hydrophobic portion and cationic site of the molecule to bind to M1 and M3 **muscarinic** receptors. Among the prepared compounds, 1-(4-methylaminobenzyl)-4-piperidyl benzhydrylcarbamate monohydrochloride (18b, YM-58790) exhibited potent **inhibitory** activity on **bladder** pressure in reflexly-evoked rhythmic contraction, comparable to oxybutynin and was approximately ten times less **inhibitory** on oxotremorine induced salivary secretion than oxybutynin in rats. Further evaluation of antimuscarinic effects on bradycardia and pressor in pithed rats, and on tremor in mice, demonstrated that YM-58790 can be useful for treatment of **urinary** urge incontinence as a **bladder**-selective M3 antagonist with fewer side effects.

L12 ANSWER 5 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998334184 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9671109
TITLE: Comparison of the in vitro and in vivo profiles of tolterodine with those of subtype-selective **muscarinic** receptor antagonists.
AUTHOR: Gillberg P G; Sundquist S; Nilvebrant L
CORPORATE SOURCE: Department of Pharmacology, Pharmacia and Upjohn, Uppsala, Sweden.
SOURCE: European journal of pharmacology, (1998 May 22) 349 (2-3) 285-92.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981006
Last Updated on STN: 19981006
Entered Medline: 19980923

AB Tolterodine [(R)-N,N-diisopropyl-3-(2-hydroxy-5 methylphenyl)-3-phenylpropanamine] is a new potent and competitive **muscarinic** receptor antagonist developed for the treatment of **urinary** urge incontinence and other symptoms of overactive **bladder.** In vivo, tolterodine exhibits functional selectivity for the **urinary bladder** over salivary glands, a profile that cannot be explained in terms of selectivity for a single **muscarinic** receptor subtype. The aim of this study was to compare the in vitro and in vivo antimuscarinic profiles of tolterodine with those of **muscarinic** receptor antagonists with distinct receptor subtype-selectivity profiles: darifenacin [(S)-2-[1-[2-(2,3 dihydrobenzofuran-5-yl)ethyl] 3 pyrrolidinyl]-2,2-d iphenylacetamide; selective for **muscarinic** M3 receptors]; UH-AH 37 (6-chloro-5,10 dihydro-5-[(1-methyl-4-piperidinyl)acetyl] 11H-dibenzo-[b ,e][1,4]diazepine-11 one; low affinity for **muscarinic** M2 receptors); and AQ-RA 741 (11-([4-[4-(diethylamino)butyl]-1-piperidinyl]acetyl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one; high affinity for **muscarinic** M2 receptors). The in vitro profiles of these compounds were in agreement with previous reports; darifenacin and UH-AH 37 demonstrated selectivity for **muscarinic** M3/m3 over M2/m2 receptors, while the converse was observed for AQ-RA 741. In vivo, AQ-RA 741 was more potent (1.4-2.7-fold) in **inhibiting urinary bladder** contraction than salivation in the anaesthetised cat (i.e., a profile similar to that of tolterodine [2.5-3.3-fold]), while darifenacin and UH-AH 37 showed the reverse selectivity profile (0.6 0.8 and 0.4-0.5-fold, respectively). The results confirm that it is possible to separate the antimuscarinic effects on **urinary bladder** and salivary glands in vivo. The data on UH-AH 37 and darifenacin support the view that a selectivity for **muscarinic** M3/m3 over M2/m2 receptors may result in a more pronounced effect on salivation than on **bladder** contraction. The data on AQ-RA 741 may indicate that **muscarinic** M2/m2 receptors may have a role in **bladder** contraction.

L12 ANSWER 6 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998332162 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9669499
TITLE: Evidence for purinergic neurotransmission in the **urinary bladder** of pithed rats.
AUTHOR: Hegde S S; Mandel D A; Wilford M R; Briaud S; Ford A P; Eglen R M
CORPORATE SOURCE: Center for Biological Research, Roche Bioscience, Palo Alto, CA 94304, USA.. sharath.hegde@roche.com
SOURCE: European journal of pharmacology, (1998 May 15) 349 (1) 75-82.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980914

AB The purpose of this study was to investigate the contribution of adenosine-5'-triphosphate (ATP) to segmental (L6-S2) spinal electrical stimulation evoked increases in intra-vesical pressure in pithed rats. Exogenous ATP and substance P produced dose-dependent increases in intra-vesical pressure (ED10 mmHg (dose required to elicit 10 mmHg increase in intra vesical pressure)= 1.7 mg/kg and 1.1 microg/kg, i.v., respectively). Desensitisation (or antagonism) of P2x purinoceptors with alpha,beta-methylene ATP (alpha,beta-meATP; 30 microg/kg per min, i.v.) or pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS; 10 mg/kg, i.v.) significantly ($p < 0.05$) antagonized the intra vesical pressure responses to ATP (> 8 and 3.6-fold increase in ED10 mmHg, respectively) but had no significant effect on intra-vesical pressure responses to substance P. Spinal stimulation evoked frequency-dependent increases in intra-vesical pressure (EF20 mmHg (frequency required to produce 20 mmHg increase in intra-vesical pressure) = 3.4 Hz). Blockade of **muscarinic** cholinoceptors and adrenoceptors with atropine (3 mg/kg, i.v.), propranolol (3 mg/kg, i.v.) and phentolamine (10 mg/kg, i.v.) produced marginal attenuation of the intra-vesical pressure responses to spinal stimulation indicating a major non-adrenergic non cholinergic (NANC) component in the overall response. The NANC responses were significantly ($p < 0.05$) antagonized by alpha,beta-meATP (30 microg/kg per min, i.v.) and PPADS (10 mg/kg, i.v.) (> 2.6-fold increase in EF20 mmHg), consistent with involvement of a purinergic neurotransmitter, presumably ATP. Comparative studies in young (4-6 months) and old (21-23 months) Fischer rats revealed no age dependent changes in the relative contribution of the cholinergic and purinergic systems, with the latter being the dominant one. These findings suggest that purinergic neurotransmission, presumably mediated by ATP acting via P2x purinoceptors, represents a major component of excitatory innervation to the **urinary bladder** in pithed rats.

L12 ANSWER 7 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998288631 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9626942
TITLE: Prejunctional facilitatory and **inhibitory** modulation of parasympathetic nerve transmission in the rabbit **urinary bladder.**
AUTHOR: Tobin G; Sjogren C
CORPORATE SOURCE: Department of Pharmacology, Institute of Physiology and Pharmacology, University of Goteborg, Sweden.. gunnar.tobin@odontologi.gu.se
SOURCE: Journal of the autonomic nervous system, (1998 Feb 5) 68 (3) 153-6.
Journal code: 8003419. ISSN: 0165-1838.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980813

AB Release of [3H]choline and muscle contraction in response to electrical field stimulation were measured from rabbit detrusor muscle strips previously loaded with [3H]choline. The importance of different stimulation frequencies (1 and 10 Hz) for activating either facilitatory or **inhibitory** prejunctional effects was examined in the presence of **muscarinic** and adrenergic (alpha2) receptor selective substances. At 1 Hz, neither [3H]choline overflow nor contraction was affected by the M1-selective receptor antagonist pirenzepine (10(-7) M), whereas overflow and contraction decreased at 10 Hz. The M1-selective receptor agonist McN-A-343 (10(-6) M) caused no significant changes except for reducing contractions at 10 Hz. The M2-selective receptor antagonist methoctramine (10(-6) M), on the other hand, increased overflow as well as contraction at both frequencies, most conspicuously at 1 Hz. Atropine (10(-7) M) caused a significant increase with respect to overflow only at 1 Hz, while quite the opposite effect occurred with respect to contractions (reduced only at 10 Hz). Clonidine (10(-6) M) induced **inhibition** of [3H]choline overflow at 10 Hz only, but without significantly changing contractile responses. The results show that in the rabbit **urinary bladder** a **muscarinic** autoreceptor mediated **inhibition** (M2) of the transmitter release dominates during low frequency stimulation and that a facilitation (M1) may be present at stimulations with higher frequencies. However, this amplification may also be influenced by alpha2 adrenoceptor mediated **inhibition.**

L12 ANSWER 8 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998287656 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9624560
TITLE: Pharmacologic actions of temiverine (p-INN) and its active metabolite, RCC 36, on isolated human **urinary bladder** muscle.
AUTHOR: Kikukawa H; Yoshida M; Wada Y; Nishi K; Ueda S
CORPORATE SOURCE: Department of Urology, Kumamoto University School of Medicine, Japan.
SOURCE: International journal of urology : official journal of the Japanese Urological Association, (1998 May) 5 (3) 268-75.
Journal code: 9440237. ISSN: 0919-8172.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980817

AB BACKGROUND: Temiverine (p-INN) is a newly synthesized drug that is expected to have anticholinergic action. We investigated the pharmacologic actions of temiverine and its active metabolite, RCC 36, on isolated human **bladder.** METHODS: Effects of temiverine and RCC-36 on the detrusor contractions induced by acetylcholine, potassium chloride (KCl), calcium chloride (CaCl2), and electric field stimulation were evaluated using the muscle-bath technique, and compared with the effects of atropine and oxybutynin. RESULTS: Atropine (10(-9) to 10(6) mol/L), oxybutynin (10(-8) to 10(-5) mol/L), temiverine (10(-8) to 10(-5) mol/L), and RCC-36 (10(-8) to 3 x 10(-6) mol/L) caused a parallel shift to the right of the concentration-response curves to acetylcholine stimulation. The rank order of pA2 value was atropine > oxybutynin = RCC 36 > temiverine. Atropine did not suppress the maximum contractile response to acetylcholine, but the other drugs significantly suppressed this at the higher concentrations. Each drug caused a concentration-dependent **inhibition** of KCl (80 mmol/L)-, and CaCl2 (5 mmol/L)-induced contractile responses. Rank order of maximum **inhibition** was RCC-36 = temiverine > oxybutynin > atropine. Each drug caused a concentration-dependent **inhibition** of electric field-induced contraction with or without 10(-6) mol/L atropine pretreatment. Maximum **inhibitions** of temiverine and RCC-36 were significantly greater than that of oxybutynin. CONCLUSION: Atropine, oxybutynin, temiverine, and RCC-36 have different efficacies and potencies of anticholinergic and calcium antagonistic activity on isolated human detrusor muscles. Furthermore, temiverine and RCC 36 have significant **inhibitory** actions toward the atropine resistant part of contractions, which may be related to the calcium antagonistic actions of these compounds.

L12 ANSWER 9 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998280590 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9617596
TITLE: Tolterodine.
AUTHOR: Hills C J; Winter S A; Balfour J A
CORPORATE SOURCE: Adis International Limited, Chester, England and Auckland, New Zealand.
SOURCE: Drugs, (1998 Jun) 55 (6) 813-20; discussion 821-2. Ref: 39
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980914

AB Tolterodine is a competitive **muscarinic** receptor antagonist which has recently been launched for the treatment of overactive **bladder**. Tolterodine shows functional selectivity for the **bladder** over the salivary glands in vivo, which is not attributable to **muscarinic** receptor subtype selectivity. It is as potent as oxybutynin in **inhibiting bladder** contraction, but is much less potent in **inhibiting** salivation, suggesting that it may have less propensity to cause dry mouth in clinical use. In patients with overactive **bladder**, toleterodine significantly reduces the frequency of micturition and number of incontinence episodes, while increasing the average volume voided. The onset of pharmacological action of tolterodine is < 1 hour and therapeutic efficacy is maintained during long term treatment. In comparative trials, tolterodine and oxybutynin are equivalent in terms of efficacy. However, tolterodine is significantly better tolerated than oxybutynin, particularly with respect to the incidence and severity of dry mouth. No clinically relevant ECG changes have been noted with tolterodine.

L12 ANSWER 10 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998178614 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9519799
TITLE: Characterization of **muscarinic** receptors mediating the contraction of the **urinary** detrusor muscle in cynomolgus monkeys and guinea pigs.
AUTHOR: Lai F M; Cobuzzi A; Spinelli W
CORPORATE SOURCE: Cardiovascular/Metabolic Diseases, Wyeth-Ayerst Research, Princeton, NJ 08543-8000, USA.
SOURCE: Life sciences, (1998) 62 (13) 1179-86.
Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980406

AB We have characterized in vitro the **muscarinic** receptors mediating the contraction of the detrusor muscle in Cynomolgus monkeys and guinea pigs using carbachol as the agonist and 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP, M3-selective), methoctramine (M2-selective) and pirenzepine (M1 selective) as the antagonists. Carbachol induced a concentration-dependent contraction of the detrusor muscle of monkey and guinea pig yielding similar pD2 values of 6.67+/-0.03 (n=50) and 6.77+/-0.06 (n=36), respectively. In the detrusor muscle of Cynomolgus monkey, all antagonists produced a concentration-dependent **inhibition** of carbachol-induced contractions, without decreasing the maximal response. Schild plot analysis yielded slopes not different from unity for all antagonists. The order of antagonist potency was: 4-DAMP (pA2=8.96)>pirenzepine (pA2=6.66)>methoctramine (pA2=6.03), suggesting that M3 receptors have a dominant role in mediating detrusor contraction. In the detrusor muscle of the guinea pig, 4-DAMP and pirenzepine, but not methoctramine, produced a concentration dependent **inhibition** of the carbachol induced contractions, without decreasing the maximal response. Schild plot analysis yielded a slope not different from unity for 4-DAMP and pirenzepine. 4-DAMP (pA2=9.07) had a higher potency than pirenzepine (pA2=6.66), a finding consistent with previously published data. The present study shows that in Cynomolgus monkey stimulation of the M3 subtype is dominant in mediating detrusor contraction upon carbachol stimulation.

L12 ANSWER 11 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998147266 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9486312
TITLE: Prejunctional M1 facilitory and M2 **inhibitory muscarinic** receptors mediate rat **bladder** contractility.
AUTHOR: Braverman A S; Kohn I J; Luthin G R; Ruggieri M R
CORPORATE SOURCE: Department of Urology, Temple University School of Medicine, Philadelphia 19140, USA.
CONTRACT NUMBER: RO1-DK39086 (NIDDK)
RO1-DK43333 (NIDDK)
SOURCE: American journal of physiology, (1998 Feb) 274 (2 Pt 2) R517-23.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 19980326
Entered Medline: 19980317

AB Subtype-selective **muscarinic** antagonists effects on carbachol-induced and electric field-stimulated contractility of rat **bladder** were compared in vitro. Schild plot analysis of cumulative carbachol dose response curves in the presence of antagonists was consistent with M3-mediated **bladder** contractions. However, nerve-evoked contractions were **inhibited** 15% at 30 Hz ($P < 0.01$) by 10 nM pirenzepine (M1-selective antagonist), whereas 10 nM methoctramine (M2-selective antagonist) increased these contractions by 17% at 30 Hz ($P < 0.01$). Identical doses had no effect on carbachol induced contractions, indicating prejunctional M1 facilitory and M2 **inhibitory** receptors. m1 Receptors could not be identified by subtype-selective antibodies, nor could the m1 transcript be identified by Northern hybridization. However, m1, m2, m3, and m4 transcripts were identified in rat **bladder** using the reverse transcriptase polymerase chain reaction, providing support for the existence of the m1 subtype. In conclusion, strong evidence is provided for the existence of prejunctional M1 facilitory and M2 **inhibitory** and postjunctional M3 receptors modulating contractility in the rat **urinary bladder.**

L12 ANSWER 12 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998136057 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9477190
TITLE: **Muscarinic** receptor subtypes and receptor coupled phosphatidylinositol hydrolysis in rat **bladder** smooth muscle.
AUTHOR: Mimata H; Nomura Y; Emoto A; Latifpour J; Wheeler M; Weiss R M
CORPORATE SOURCE: Department of Urology, Oita Medical University, Japan.
SOURCE: International journal of urology : official journal of the Japanese Urological Association, (1997 Nov) 4 (6) 591-6.
Journal code: 9440237. ISSN: 0919-8172.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980408

AB BACKGROUND: The purpose of this study was to evaluate the **muscarinic** receptor subtypes expressed in rat **bladder** smooth muscle and characterize the **muscarinic** receptor-coupled phosphatidylinositol (PI) hydrolysis in order to clarify the first step of **bladder** smooth muscle contraction. METHODS: Expressions of mRNAs of **muscarinic** receptor subtypes were examined by Northern blot analysis. Changes in the mass of inositol 1,4,5-trisphosphate (IP3) and the **inhibitory** effects of **muscarinic** subtype specific antagonists on PI hydrolysis were determined after carbachol stimulation. RESULTS: mRNAs of m2 and m3 genes, encoding M2 and M3 receptors, were expressed in rat **bladder** smooth muscle. Carbachol produced a rapid increase of IP3, which returned to the basal level within 30 seconds. 4-Diphenylacetoxyl N-methylpiperidine methiodide (4-DAMP; M1 and M3 antagonist) strongly **inhibited** the PI hydrolysis, but methoctramine (M2 antagonist) partially **inhibited** it at 10(-4) mol/L. The IC50 value for atropine was 9.5 x 10(-9) mol/L, for pirenzepine 6.4 x 10(6) mol/L, and for 4-DAMP 1.5 x 10(-7) mol/L. CONCLUSION: M2 and M3 receptors are expressed in rat **urinary bladder**. Only M3 receptor was involved in the production of IP3, which might induce the initial phase of contractile response in rat **bladder** smooth muscle after carbachol stimulation.

L12 ANSWER 13 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998118820 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9457494
TITLE: Effect of choline ester analogues, noradrenaline and nifedipine on normal and hypertrophied human **urinary bladder** detrusor muscle.
AUTHOR: King J A; Huddart H; Staff W G
CORPORATE SOURCE: Division of Biological Sciences, Lancaster University, UK.
SOURCE: General pharmacology, (1998 Jan) 30 (1) 131-6.
Journal code: 7602417. ISSN: 0306-3623.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980319
Last Updated on STN: 19980319
Entered Medline: 19980312

AB 1. Acetylcholine, bethanechol, carbachol and propionylcholine were all agonists of normal human detrusor smooth muscle. The order of potency was found to be carbachol > acetylcholine > bethanechol > propionylcholine. 2. In hypertrophied detrusor smooth muscle carbachol was more potent than acetylcholine, but hypertrophied detrusor preparations were less sensitive to carbachol than normal detrusor smooth muscle. 3. Noradrenaline had no direct effect on either normal or hypertrophied detrusor muscle, but it had a reversible **inhibitory** effect on the spontaneous contractile activity of normal detrusor preparations. Hypertrophied detrusor preparations usually lacked such spontaneous activity. 4. In calcium-free saline, agonist-induced responses of both normal and hypertrophied detrusor muscle were dramatically reduced indicating that choline ester activity in the muscles was strongly dependent upon extracellular calcium. 5. Nifedipine at 10(-5) mol l-1 **inhibited** acetylcholine responses and K(+)-induced contractures of both normal and hypertrophied detrusor muscles. Acetylcholine-induced responses of normal detrusor preparations were much more sensitive to **inhibition** by nifedipine than were the responses of hypertrophied detrusor muscle. 6. The properties and densities of both the **muscarinic** cholinoreceptors and calcium channels appear to have been altered by the hypertrophic response secondary to benign prostatic hyperplasia.

L12 ANSWER 14 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998088162 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9426756
TITLE: The overactive **bladder**: pharmacologic basis of drug treatment.
AUTHOR: Andersson K E
CORPORATE SOURCE: Department of Clinical Pharmacology, Lund University Hospital, Sweden.
SOURCE: Urology, (1997 Dec) 50 (6A Suppl) 74-84; discussion 85-9.
Ref: 107
Journal code: 0366151. ISSN: 0090-4295.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980129

AB OBJECTIVES: To provide an overview of the basis for drug treatment of the overactive **bladder**. METHODS: Published information is evaluated. RESULTS: The causes of **bladder** overactivity are not known, but theoretically, increased afferent activity, decreased **inhibitory** control in the central nervous system (CNS) or peripheral ganglia, and increased sensitivity of the detrusor to efferent stimulation may be involved. Several CNS transmitters can modulate voiding, but few useful drugs with a defined CNS site of action have been developed. Drugs that stimulate gamma-aminobutyric acid receptors are used clinically. Potentially, drugs affecting opioid, 5-hydroxytryptamine, norepinephrine, dopamine, and glutamatergic receptors and mechanisms can be developed, but a selective action on the lower **urinary** tract may be difficult to obtain. Traditionally, drugs used for treatment of **bladder** overactivity have had a peripheral site of action, mainly efferent neurotransmission or the detrusor itself. Antimuscarinic drugs, beta-adrenoceptor agonists, alpha-adrenoceptor antagonists, drugs affecting membrane channels, prostaglandin synthetase **inhibitors**, and several other agents have been used with limited success. New information on the alpha-adrenoceptor and **muscarinic** receptor subtypes in the human detrusor has emerged and may be the basis for the development of new compounds with effects on **bladder** overactivity. Decreasing afferent activity seems an attractive therapeutic approach, and drugs affecting afferent nerves by causing release of tachykinins, such as capsaicin and analogs, as well as agents blocking tachykinin receptors, may be of therapeutic interest. CONCLUSIONS: New drugs, specifically designed for the treatment of **bladder** overactivity, are desirable.

L12 ANSWER 15 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998075781 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9413860
TITLE: Subcellular distribution of SERCA and calcium-activated ATPase in rabbit and human **urinary bladder** smooth muscle.
AUTHOR: Levin R M; Nicholas T J; Snitkoff G G; Mandell J; Russell D; Wilbur H J; Mogavero L J
CORPORATE SOURCE: Department of Biological Science, Albany College of Pharmacy, NY 12208, USA.
CONTRACT NUMBER: 1R01 DK 26508 (NIDDK)
SOURCE: Pharmacology, (1997 Dec) 55 (6) 309-16.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980203

AB Previous studies have demonstrated that calcium storage and release from IP3-dependent sites in the sarcoplasmic reticulum play an important role in the contractile response of the rabbit **urinary bladder** to both field stimulation (mediated via neurotransmitter release) and bethanechol (direct **muscarinic** stimulation). In view of the importance of SERCA (see text) in **urinary bladder** smooth muscle function, we studied the distribution of SERCA by two methods; using Western blotting to quantitate the protein concentration and by enzyme analysis using thapsigargin to specifically **inhibit** SERCA. Rabbit and human samples of **urinary bladder** smooth muscle were homogenized and the homogenate separate into three particulate fractions by different centrifugation: the cell wall-nuclear, mitochondrial, and microsomal. The protein concentration of these three particulate fractions was determined and the SERCA protein level quantitated by Western blotting using SERCA-2 antibodies. The calcium ATPase activity was quantitated using standard enzymatic analysis and the thapsigargin sensitivity determined. The results demonstrated that (1) the concentration of SERCA was significantly greater in the microsomal fraction than in either of the other fractions for both rabbit and human **bladder** smooth muscle; (2) the enzymatic activities of both total calcium-activated ATPase and thapsigargin-sensitive calcium ATPase were evenly divided among the three fractions, and (3) the enzymatic activity of both total calcium-activated ATPase and thapsigargin sensitive calcium ATPase of the rabbit exceeded that of the human. In conclusion, the distribution of SERCA and calcium ATPase of the rabbit **bladder** smooth muscle was similar to that in the human **bladder** smooth muscle, although activities in rabbit were significantly greater than those of human tissue.

L12 ANSWER 16 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998063137 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9400490
TITLE: Bethanechol activates a post-receptor negative feedback mechanism in rabbit **urinary bladder** smooth muscle.
AUTHOR: Shenfeld O Z; Morgan C W; Ratz P H
CORPORATE SOURCE: Department of Urology, Eastern Virginia Medical School, Norfolk 23501, USA.
SOURCE: Journal of urology, (1998 Jan) 159 (1) 252-7.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980116
Last Updated on STN: 19980116
Entered Medline: 19971229

AB PURPOSE: Recent studies using vascular and gut smooth muscles indicate that contractile receptor agonists may activate post-receptor down-regulatory mechanisms causing a temporary reduction in the strength of subsequent contractions. Our data indicate a similar mechanism exists in detrusor smooth muscle of the **urinary bladder.** MATERIALS AND METHODS: Each isolated strip of female rabbit detrusor was placed in a tissue bath, secured to an isometric force transducer, and length-adjusted until depolarization with 110 mM KCl produced a maximum contraction (S0). Subsequent contractions were normalized to S0 (S/S0) or to a first stimulus with 30 mM KCl or caffeine (S/S1). Tissues were pretreated with the **muscarinic** receptor agonist, bethanechol (BE), then stimulated with KCl, caffeine, or Bay k 8644 to identify potential post-receptor down regulation. RESULTS: Contractions induced by 30 mM KCl had three phases labeled fast peak (FP), slow peak (SP) and steady state (SS). In tissues exposed for 30 min. to a maximum BE concentration then washed for 5 min., the KCl-induced FP and SP, but not SS, responses were reduced by approximately 40%. Smaller reductions in peak KCl-induced contractions occurred in tissues pretreated for a shorter duration or with a 100-fold lower BE concentration. This down-regulation induced by bethanechol pretreatment was reversible, lasting approximately 1-2 h. Not only were KCl-induced contractions reduced by BE pretreatment, but also those produced by the intracellular Ca(2+)-mobilizer, caffeine, and the L-type Ca2+ channel agonist, Bay k 8644. CONCLUSIONS: Pretreatment of isolated strips of rabbit detrusor with a **muscarinic** receptor agonist produced short-term down-regulation of KCl-induced peak contractions that may have involved **inhibition** of both influx of extracellular Ca2+ and release of intracellular Ca2+. Reductions in the degree of this novel modulatory response during disease conditions and aging could enhance contractile activity, possibly causing detrusor instability.

09/ 960,477

L12 ANSWER 17 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998049688 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9388365
TITLE: Autoradiographic localization of **muscarinic** receptors in diabetic rat **bladder.**
AUTHOR: Saito M; Nakamura I; Miyagawa I
CORPORATE SOURCE: Department of Urology, Tottori University School of Medicine.
SOURCE: Nippon Hinyokika Gakkai zasshi. japanese journal of urology, (1997 Oct) 88 (10) 858-67.
Journal code: 2984841R. ISSN: 0021-5287.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 19980122
Entered Medline: 19971231

AB PURPOSE: We evaluated the alterations of density, localization and subtype specificity of **muscarinic** receptors in experimentally-induced diabetic rat **bladder.** METHODS: Five groups of rats were maintained for sixteen weeks 1) diabetic, 2) diabetic insulin-treated (insulin started 8 weeks after the onset of diabetes), 3) sucrose-fed diuretic, 4) sucrose-removed and 5) age matched controls. We used radioligand binding technique and light microscopic autoradiography to define the density and distribution of **muscarinic** receptors in the rat **urinary bladder.** RESULTS & CONCLUSION: Saturation experiments showed an increase in the density of **muscarinic** receptors in the **bladders** of diabetic and diuretic rats compared with age matched controls. Insulin treatment partially reversed the up-regulatin of **muscarinic** receptors in rat **urinary bladder.** Autoradiographic studies also indicated that **muscarinic** receptors were located in all layers of the **bladder** muscularis. The muscularis of the **bladder** dome contained higher densities of **muscarinic** receptors than that of the **bladder** base. Lack of [3H]QNB binding to transitional epithelium, lamina propria, and tunica adventitia suggests an absence of **muscarinic** receptors in these regions. **Inhibition** of [3H]QNB binding to the **bladder** sections by selective **muscarinic** antagonists indicated existence of the M2 and M3 receptor subtypes in the muscularis of the rat **bladder.**

L12 ANSWER 18 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998019306 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9353395
TITLE: M4 **muscarinic** autoreceptor-mediated **inhibition** of -3H-acetylcholine release in the rat isolated **urinary bladder.**
AUTHOR: D'Agostino G; Barbieri A; Chiossa E; Tonini M
CORPORATE SOURCE: Institute of Pharmacology, School of Pharmacy, University of Pavia, Pavia, Italy.
SOURCE: Journal of pharmacology and experimental therapeutics, (1997 Nov) 283 (2) 750 6.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971208

AB A pharmacological analysis was carried out in the rat **urinary bladder** to assess the nature of **muscarinic** receptors subtypes functionally involved in the negative feedback mechanism regulating acetylcholine (ACh) secretion from postganglionic cholinergic nerve terminals and in smooth muscle contraction. **Bladder** strips were preincubated with 3H-choline, and the electrically evoked [3H]ACh release was detected simultaneously with contraction in the absence of acetylcholinesterase **inhibitors.** The effects were compared of seven **muscarinic** antagonists on [3H]ACh secretion (prejunctional effect) and muscle contraction (postjunctional effect). The rank order of postjunctional potencies (-log EC50) for the seven antagonists (atropine > 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP) > hexahydrosiladiphenidol hydrochloride (HHSiD) > tripitramine > pirenzepine > AF-DX-116 > methoctramine) as well as their postjunctional affinity estimates (pA2) are in keeping with the notion that **muscarinic** receptors responsible for **bladder** contraction belong to the M3 subtype. The M3 subtype-preferring 4-DAMP and HHSiD did not discriminate between prejunctional and postjunctional effects. The M2/M4 subtype-preferring antagonists tripitramine, methoctramine and AF-DX 116 were more potent in facilitating the evoked [3H]ACh release than in **inhibiting** the contractile response. The rank order of prejunctional potencies was atropine > 4-DAMP > tripitramine > HHSiD > methoctramine > AF-DX 116 > pirenzepine, indicating the involvement of M4 receptors. Furthermore, when potency relationship was determined by correlating prejunctional -log EC50 values with published constants for cloned and natives **muscarinic** receptor subtypes, the correlations were significant for both M4 and M5 subtypes, but the best correlation found ($P < .001$) was for the M4 subtype. These findings suggest that the negative feedback mechanism **inhibiting** the release of ACh in the rat **urinary bladder** is mediated by prejunctional autoreceptors of the M4 subtype.

L12 ANSWER 19 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998015289 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9353847
TITLE: Antimuscarinic potency and **bladder** selectivity of PNU-200577, a major metabolite of tolterodine.
AUTHOR: Nilvebrant L; Gillberg P G; Sparf B
CORPORATE SOURCE: Medical Department Urology, Pharmacia & Upjohn AB, Uppsala, Sweden.
SOURCE: Pharmacology & toxicology, (1997 Oct) 81 (4) 169-72.
Journal code: 8702180. ISSN: 0901-9928.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980130

AB PNU-200577 (labcode DD 01 [(R) N, N-diisopropyl-3-(2-hydroxy-5 hydroxymethylphenyl)-3-phenylpropanamine) is a major pharmacologically active metabolite of tolterodine, a new **muscarinic** receptor antagonist intended for the treatment of an overactive **bladder.** In vitro, PNU-200577 produced a competitive and concentration-dependent **inhibition** of carbachol-induced contraction of guinea-pig isolated **urinary bladder** strips (KB = 0.84 nM; pA2 = 9.14). In vivo, PNU-200577 was significantly more potent at **inhibiting** acetylcholine-induced **urinary bladder** contraction than electrically induced salivation in the anaesthetised cat (ID50 15 and 40 nmol.kg-1, respectively; $P < 0.01$). In radioligand binding studies carried out in homogenates of guinea pig tissues and Chinese hamster ovary cell lines expressing human **muscarinic** m1-m5 receptors, PNU-200577 was not selective for any **muscarinic** receptor subtype. Thus, PNU-200577 is similar to tolterodine in terms of antimuscarinic potency, functional selectivity for the **urinary bladder** in vivo and absence of selectivity for **muscarinic** receptor subtypes in vitro. The results of this study clearly indicate that PNU-200577 contributes to the therapeutic action of tolterodine, in view of its high antimuscarinic potency, similar serum concentration and lower degree of protein binding.

L12 ANSWER 20 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998006873 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9347324
TITLE: Anticholinergic and calcium antagonistic activities of NS-21 contribute to the **inhibition** of rat **urinary bladder** contractions.
AUTHOR: Hamada K; Sasaki Y; Taniguchi N; Fukui H; Miyatsuka Y; Kimura Y; Ukai Y; Yoshikuni Y; Kimura K
CORPORATE SOURCE: Research Laboratories, Nippon Shinyaku Co., Ltd., Kyoto, Japan.
SOURCE: General pharmacology, (1997 Nov) 29 (5) 771-8.
Journal code: 7602417. ISSN: 0306-3623.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971204

AB 1. Pharmacological characteristics of NS-21 and its main metabolite, RCC-36, in the **inhibition** of rat **urinary bladder** contractions were investigated both in vitro and in vivo. 2. NS-21 and RCC-36 **inhibited muscarinic** receptor bindings to rat **bladder** membranes with [3H]3-quinuclidinyl bezilate (pKi 6.19 and 7.24, respectively), whereas they failed to **inhibit** the following receptor bindings: adrenergic (alpha 1, alpha 2 and beta), dopaminergic (D1 and D2), adenosine (A1 and A2), histaminergic (H1) and opioid (mu, delta and kappa) receptors. 3. NS-21 and RCC-36 suppressed carbachol induced contractions of isolated rat detrusor strips in competitive (pA2 6.80 and 7.93, respectively) and noncompetitive (pD'2 5.93 and 5.77, respectively) manners. 4. NS-21 and RCC-36 **inhibited** CaCl2-induced contractions of rat detrusor strips in the presence of 100 mM K+ (pIC50 6.54 and 5.76, respectively), as well as the 100 mM K(+)-induced 45Ca influx into the isolated **bladder** strips at > or = 1 microM. 5. Electrical stimulation of the peripheral end of the pelvic nerve in anesthetized rats induced **bladder** contractions composed of two phases: an initial phasic contraction that was weakly suppressed by atropine, and a tonic contraction that was strongly suppressed by atropine. NS-21 suppressed both contractions to the same degree (ID50 2.65 and 2.19 mg/kg, i.v., respectively). RCC 36 suppressed the tonic contraction (ID50 1.20 mg/kg, i.v.) more markedly than the initial contraction (ID50 7.43 mg/kg, i.v.). 6. These results suggest that NS-21 and RCC-36 suppressed **bladder** contractions owing to their anticholinergic and calcium antagonistic activities.

L12 ANSWER 21 OF 121 MEDLINE on STN
ACCESSION NUMBER: 1998004388 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9346402
TITLE: Subcellular distribution of SERCA and calcium-activated ATPase in rabbit and human **urinary bladder** smooth muscle.
AUTHOR: Levin R M; Nicholas T J; Snitkoff G G; Mandell J; Russell D; Wilbur H J; Mogavero L J
CORPORATE SOURCE: Albany College of Pharmacy, Stratton Veterans Affairs Medical Center, N.Y. 12208, USA.
CONTRACT NUMBER: 1RO1 DK 26508 (NIDDK)
SOURCE: Pharmacology, (1997 Sep) 55 (3) 136-43.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971119

AB Previous studies have demonstrated that calcium storage and release from IP-3-dependent sites in the sarcoplasmic reticulum play an important role in the contractile response of the rabbit **urinary bladder** to both field stimulation (mediated via neurotransmitter release) and bethanechol (direct **muscarinic** stimulation). In view of the importance of SERCA in **urinary bladder** smooth muscle function, we studied the distribution of SERCA by two methods: using Western blotting to quantitate the protein concentration and by enzyme analysis using thapsigargin to specifically **inhibit** SERCA. Rabbit and human samples of **urinary bladder** smooth muscle were homogenized and the homogenate separated into three particulate fractions by differential centrifugation: nuclear-cell wall, mitochondrial, and microsomal. The protein concentration of these three particulate fractions was determined and the SERCA protein level quantitated by Western blotting using SERCA-2 antibodies. The calcium-ATPase activity was quantitated using standard enzymatic analysis and the thapsigargin sensitivity determined. The results demonstrated that: (1) the concentration of SERCA was significantly greater in the microsomal fraction than in either of the other fractions for both rabbit and human **bladder** smooth muscle; (2) the enzymatic activities of both total calcium-activated ATPase and thapsigargin-sensitive calcium ATPase were evenly divided among the three fractions, and (3) the enzymatic activity of both total calcium-activated ATPase and thapsigargin-sensitive calcium ATPase of the rabbit exceeded that of the human. In conclusion, the distribution of SERCA and calcium-ATPase of the rabbit **bladder** smooth muscle was similar to that in the human **bladder** smooth muscle, although activities in rabbit were significantly greater than those of human tissue.

L12 ANSWER 22 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97344033 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9200560
TITLE: Tolterodine- a new **bladder**-selective antimuscarinic agent.
AUTHOR: Nilvebrant L; Andersson K E; Gillberg P G; Stahl M; Sparf B
CORPORATE SOURCE: Medical Department Urology, Pharmacia & Upjohn AB, Uppsala, Sweden.
SOURCE: European journal of pharmacology, (1997 May 30) 327 (2-3) 195-207.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970902
Last Updated on STN: 19970902
Entered Medline: 19970818

AB Tolterodine is a new **muscarinic** receptor antagonist intended for the treatment of **urinary** urge incontinence and other symptoms related to an overactive **bladder.** The aim of the present study was to compare the antimuscarinic properties of tolterodine with those of oxybutynin, in vitro and in vivo. Tolterodine effectively **inhibited** carbachol-induced contractions of isolated strips of **urinary bladder** from guinea pigs (K(B) 3.0 nM; pA2 8.6; Schild slope 0.97) and humans (K(B) 4.0 nM; pA2 8.4; Schild slope 1.04) in a concentration-dependent, competitive manner. The affinity of tolterodine was similar to that derived for oxybutynin (K(B) 4.4 nM; pA2 8.5; Schild slope 0.89) in the guinea-pig **bladder.** Tolterodine (21-2103 nmol/kg (0.01-1 mg/kg); intravenous infusion) was significantly more potent in **inhibiting** acetylcholine-induced **urinary bladder** contraction than electrically-induced salivation in the anaesthetised cat. In contrast, oxybutynin displayed the opposite tissue selectivity. Radioligand binding data showed that tolterodine bound with high affinity to **muscarinic** receptors in **urinary bladder** (K(i) 2.7 nM), heart (K(i) 1.6 nM), cerebral cortex (K(i) 0.75 nM) and parotid gland (K(i) 4.8 nM) from guinea pigs and in **urinary bladder** from humans (K(i) 3.3 nM). Tolterodine and oxybutynin were equipotent, except in the parotid gland, where oxybutynin bound with 8-times higher affinity (K(i) 0.62 nM). Binding data on human **muscarinic** m1-m5 receptors expressed in Chinese hamster ovary cells showed that oxybutynin, in contrast to tolterodine, exhibits selectivity (10-fold) for **muscarinic** m3 over m2 receptors. The K(B) value determined for oxybutynin (4.4 nM) in functional studies on guinea-pig **bladder** correlated better with the binding affinity at **muscarinic** M2/m2 receptors (K(i) 2.8 and 6.7 nM) than at **muscarinic** M3/m3 receptors (K(i) 0.62 and 0.67 nM). The tissue selectivity demonstrated for tolterodine in vivo cannot be attributed to selectivity for a single **muscarinic** receptor subtype. However, the combined in vitro and in vivo data on tolterodine and oxybutynin may indicate either that **muscarinic** M3/m3 receptors in glands are more sensitive to blockade than those in **bladder** smooth muscle, or that **muscarinic** M2/m2 receptors contribute to **bladder** contraction.

L12 ANSWER 23 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97308396 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9165622
TITLE: Etiology of **bladder** dysfunction secondary to partial outlet obstruction. Calcium disregulation in **bladder** power generation and the ability to perform work.
AUTHOR: Levin R M; Yu H J; Kim K B; Longhurst P A; Wein A J; Damaser M S
CORPORATE SOURCE: Division of Urology, University of Pennsylvania, USA.
CONTRACT NUMBER: 5 T32-DK07708 (NIDDK)
RO1 DK 46508 (NIDDK)
SOURCE: Scandinavian journal of urology and nephrology. Supplementum, (1997) 184 43-50.
Journal code: 0153034. ISSN: 0300 8886.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970807

AB Similar to all smooth muscle, contraction of **urinary bladder** smooth muscle depends upon a rise in intracellular free calcium, which results from both calcium influx from extracellular spaces and calcium release from intracellular stores (calcium-induced calcium release [CICR]). Recent studies from our laboratory demonstrate that one of the major dysfunctions induced by partial outlet obstruction is a marked reduction in the participation of CICR (from IP3-sensitive and IP3-insensitive sites on the sarcoplasmic reticulum [SR]) during stimulation by both field stimulation (neurotransmitter release) and by direct **muscarinic** stimulation (bethanechol). Experimentally, rabbit **urinary bladder** function can be evaluated using an isolated whole **bladder** model. The current study utilizes the isolated whole **bladder** model to compare the effects of partial outlet obstruction on the responses to field stimulation and bethanechol with the responses of normal **bladders** following **inhibition** of CICR with the combination of thapsigargin+ryanodine. The parameters measured include the magnitude of pressure generation, rate of pressure generation, time to maximal pressure generation, percent volume emptied, rate of emptying, power generation, and work performed (both total work and work per ml emptied). Partial outlet obstruction resulted in virtually identical alterations in the responses of the **bladder** to stimulation (field stimulation and bethanechol) to that of **inhibition** of CICR by thapsigargin+ryanodine. Thus, these studies provide strong support for our hypothesis that the contractile dysfunctions secondary to partial outlet obstruction are directly related to a marked **inhibition** of the CICR component of the response to both field stimulation and bethanechol.

L12 ANSWER 24 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97276408 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9130161
TITLE: Role of L- and N-type Ca2+ channels in **muscarinic** receptor-mediated facilitation of ACh and noradrenaline release in the rat **urinary bladder.**
AUTHOR: Somogyi G T; Zernova G V; Tanowitz M; de Groat W C
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh, PA 15261, USA.. somo+@pitt.edu
CONTRACT NUMBER: NIDDK-45741 (NIDDK)
SOURCE: Journal of physiology, (1997 Mar 15) 499 (Pt 3) 645-54.
Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970825
Last Updated on STN: 20000303
Entered Medline: 19970812

AB 1. 3H-Noradrenaline (NA) and 14C-acetylcholine (ACh) released by electrical field stimulation were measured simultaneously in strips from the body of rat **urinary bladder.** 2. omega-Conotoxin GVIA (omega-CgTX; 20-100 nM) suppressed the non-facilitated transmitter release evoked by intermittent stimulation (IS), whereas nifedipine (1 microM) did not affect release. 3. Continuous electrical stimulation (CS) facilitated NA and ACh release via an atropine-sensitive mechanism. omega-CgTX reduced the facilitated release of NA (44% depression) but did not affect ACh release. Nifedipine depressed ACh release (43%) but not NA release. Combined administration of nifedipine and omega-CgTX (20 nM) produced a greater suppression of NA and ACh release (86 and 91%, respectively). 4. Maximal **muscarinic** facilitation of NA (5-fold) and ACh (17-fold) release occurred following administration of eserine, an anticholinesterase agent. Release of both NA and ACh was depressed by nifedipine (70 and 83%, respectively) but not by omega-CgTX. Combined application of omega-CgTX and nifedipine elicited a further depression of NA (95%) but not ACh release. 5. When NA and ACh release was facilitated with phorbol dibutyrate (0.5 microM), nifedipine **inhibited** ACh (67%) but not NA release, whereas omega-CgTX **inhibited** NA (73%) but not ACh release. Combined administration of both Ca2+ channel blockers did not elicit greater **inhibition.** 6. Bay K 8644, the L-type Ca2+ channel activator, increased ACh release in a dose-dependent manner (up to 5-fold) but did not significantly change NA release. 7. Both omega-CgTX (20-100 nM) and nifedipine (100 nM-1 microM) significantly decreased (50-80%) the neurally evoked contractions of the **bladder** strips. 8. It is concluded that L-type Ca2+ channels play a major role in **muscarinic** facilitation of NA and ACh release in the **urinary bladder** but are not essential for non-facilitated release. Other types of Ca2+ channels, including N-type, are involved to varying degrees in non-facilitated and facilitated release under different experimental conditions.

L12 ANSWER 25 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97273337 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9127817
TITLE: Effects of ONO-2235, an aldose reductase **inhibitor**, on **muscarinic** receptors and contractile response of the **urinary bladder** in rats with streptozotocin induced diabetes.
AUTHOR: Kanda M; Eto K; Tanabe N; Sugiyama A; Hashimoto K; Ueno A
CORPORATE SOURCE: Department of Urology, Yamanashi Medical University, Japan.
SOURCE: Japanese journal of pharmacology, (1997 Mar) 73 (3) 221-8.
Journal code: 2983305R. ISSN: 0021-5198.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 19970805
Entered Medline: 19970721

AB This study was conducted to evaluate effects of the aldose reductase **inhibitor** ONO-2235 on the contractile response to acetylcholine of the **urinary bladder** dome of streptozotocin-induced diabetes mellitus (DM) rats and simultaneously observe the changes in the function and number of **muscarinic** receptors and the sorbitol content of the **bladder**. The contractile response to acetylcholine increased 51% in the DM rat **bladder** dome compared to the normal rats; however, this was attenuated to a 10% increase by administration of 100 mg/kg ONO-2235 for 2 weeks. Treatment with ONO-2235 significantly decreased the specific [3H]quinuclidinyl benzilate binding in DM rats. However there was no significant dose-dependency among the ONO-2235-treated groups. The sorbitol levels of the sciatic nerve and the **bladder** were higher in the DM rats compared to the control rats; ONO-2235 decreased the level, although it did not completely reverse them to the control level. These results suggest that an aldose reductase **inhibitor** attenuates the increase of the **muscarinic** receptor number and normalizes the enhanced contractile response to acetylcholine caused by hyperglycemia and diuresis, probably through suppression of the polyol-pathway in the DM rat **bladder** dome.

L12 ANSWER 26 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97268065 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9113359
TITLE: Functional role of M2 and M3 **muscarinic** receptors in the **urinary bladder** of rats in vitro and in vivo.
AUTHOR: Hegde S S; Choppin A; Bonhaus D; Briaud S; Loeb M; Moy T M; Loury D; Eglen R M
CORPORATE SOURCE: Department of Urogenital and Mechanistic Pharmacology, Institute of Pharmacology, Palo Alto, CA, USA.
SOURCE: British journal of pharmacology, (1997 Apr) 120 (8) 1409-18.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970709
Last Updated on STN: 19980206
Entered Medline: 19970623

AB 1. **Urinary bladder** smooth muscle is enriched with **muscarinic** receptors, the majority of which are of the M2 subtype whereas the remaining minority belong to the M3 subtype. The objective of the present study was to assess the functional role of M2 and M3 receptors in the **urinary bladder** of rat in vitro and in vivo by use of key discriminatory antagonists. 2. In the isolated **bladder** of rat, (+)-cis-dioxolane produced concentration-dependent contractions (pEC50 = 6.3) which were unaffected by tetrodotoxin (0.1 microM). These contractions were antagonized by **muscarinic** antagonists with the following rank order of affinity (pA2) estimates: atropine (9.1) > 4-diphenyl acetoxy methyl piperidine methiodide (4-DAMP) (8.9) > darifenacin (8.5) > para fluoro hexahydrosiladifenidol (p F HHSiD) (7.4) > pirenzepine (6.8) > methoctramine (5.9). These pA2 estimates correlated most favourably (r = 0.99, P < 0.001) with the binding affinity (pKi) estimates of these compounds at human recombinant **muscarinic** m3 receptors expressed in Chinese hamster ovary cells, suggesting that the receptor mediating the direct contractile responses to (+)-cis dioxolane equates with the pharmacologically defined M3 receptor. 3. As M2 receptors in smooth muscle are negatively coupled to adenylyl cyclase, we sought to determine whether a functional role of M2 receptors could be unmasked under conditions of elevated adenylyl cyclase activity (i.e., isoprenaline-induced relaxation of KCl pre-contracted tissues). **Muscarinic** M3 receptors were preferentially alkylated by exposing tissues to 4-DAMP mustard (40 nM, 1 h) in the presence of methoctramine (0.3 microM) to protect M2 receptors. Under these conditions, (+) cis-dioxolane produced concentration-dependent reversal (re-contraction) of isoprenaline-induced relaxation (pEC50 = 5.8) but had marginal effects on pinacidil-induced, adenosine 3':5'-cyclic monophosphate (cyclic AMP) independent, relaxation. The re-contractions were antagonized by methoctramine and darifenacin, yielding pA2 estimates of 6.8 and 7.6, respectively. These values are intermediate between those expected for these compounds at M2 and M3 receptors and were consistent with the involvement of both of these subtypes. 4. In urethane-anaesthetized rats, the cholinergic component (approximately 55%) of volume-induced **bladder** contractions was **inhibited** by **muscarinic** antagonists with the following rank order of

L12 ANSWER 26 OF 121 MEDLINE on STN (Continued)
potency (ID35%inh, nmol kg 1, i.v.): 4-DAMP (8.1) > atropine (20.7) > methoctramine (119.9) > darifenacin (283.3) > pirenzepine (369.1) > p F HHSiD (1053.8). These potency estimates correlated most favourably (r = 0.89, P = 0.04) with the pKi estimates of these compounds at human recombinant **muscarinic** m2 receptors. This is consistent with a major contribution of M2 receptors in the generation of volume induced **bladder** contractions, although the modest potency of darifenacin does not exclude a role of M3 receptors. Pretreatment with propranolol (1 mg kg-1, i.v.) increased the ID35%inh of methoctramine significantly from 95.9 to 404.5 nmol kg-1 but had no significant effects on the **inhibitory** responses to darifenacin. These data suggest an obligatory role of beta adrenoceptors in M2 receptor-mediated **bladder** contractions in vivo. 5. The findings of the present study suggest that both M2 and M3 receptors can cause contraction of the rat **bladder** in vitro and may also mediate reflex **bladder** contractions in vivo. It is proposed that **muscarinic** M3 receptor activation primarily causes direct contraction of the detrusor whereas M2 receptor activation can contract the **bladder** indirectly by reversing sympathetically (i.e. beta-adrenoceptor)-mediated relaxation. This dual mechanism may allow the parasympathetic nervous system, which is activated during voiding, to cause more efficient and complete emptying of the **bladder**.

L12 ANSWER 27 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97149597 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8996405
TITLE: Evidence for the presence of regional differences in the subtype specificity of **muscarinic** receptors in rabbit lower **urinary** tract.
AUTHOR: Mutoh S; Latifpour J; Saito M; Weiss R M
CORPORATE SOURCE: Section of Urology, Yale University School of Medicine, New Haven, Connecticut 06520-8041, USA.
CONTRACT NUMBER: DK 38311 (NIDDK)
DK 42530 (NIDDK)
SOURCE: Journal of urology, (1997 Feb) 157 (2) 717-21.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19970305
Entered Medline: 19970218

AB To elucidate the subtype specificity of **muscarinic** cholinergic receptors in mediating contractile responses in the lower **urinary** tract, we investigated contractile and biochemical properties of **muscarinic** receptors in **bladder** dome, **bladder** base and urethra of the rabbit. Isometric contractile response curves to increasing concentrations of carbachol were constructed in the absence and presence of various concentrations of subtype selective **muscarinic** antagonists. **Bladder** dome, **bladder** base, and urethra demonstrate different characteristics in terms of efficacy and potency with respect to carbachol-induced contractile responses. Emax values are significantly larger and ED50 values are significantly smaller in **bladder** dome and **bladder** base than in urethra. Calculation of the pA2 values, the negative logarithm of the antagonist affinity constant (KB), for a series of **muscarinic** antagonists, i.e., atropine (nonselective), pirenzepine (M1 selective), methoctramine (M2 selective), and 4 DAMP (M1/M3 selective) indicate that the carbachol-induced contractile response in **bladder** dome and **bladder** base is mediated through the M3 receptor subtype whereas the carbachol induced contractile response in urethra is probably mediated through the M1 and/or M3 and possibly M2 subtypes. **Muscarinic** cholinergic antagonists **inhibit** [3H]quinulidinyl benzilate binding to **bladder** dome, **bladder** base and urethra with the following rank order of affinities: atropine > 4-DAMP > methoctramine > pirenzepine. The binding data indicate the predominance of the M2 receptor subtype in all three regions.

L12 ANSWER 28 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97144729 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8990491
TITLE: Physiological effects of a novel bioactive agent.
AUTHOR: Hass M A; Geloso D; Leggett R E; Horan P; Levin R M
CORPORATE SOURCE: Department of Physical Science and Mathematics, Albany College of Pharmacy, NY 12208, USA.
CONTRACT NUMBER: DK-26508-15 (NIDDK)
SOURCE: Pharmacology, (1996 Nov) 53 (5) 320-7.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970620
Last Updated on STN: 19990129
Entered Medline: 19970612

AB **Urinary bladder** smooth muscle contraction can be evaluated using field stimulation (neurohumoral transmission), carbachol (**muscarinic** stimulation), and KCl (direct membrane depolarization). We recently evaluated the activity of a novel organic chemical, macrocycle-1, on the contractile responses of the **bladder** to field stimulation, carbachol, and KCl. Isolated strips of rabbit **bladder** were mounted in individual baths containing 7.5 ml Tyrode's solution. The response to FS (1-32 Hz), carbachol (1 mumol/l), and KCl (120 mmol/l) were determined in the presence and absence of 3 different concentrations of macrocycle-1. Maximal tension, the rate of tension generation, the time to maximal tension, and the rate of decay following maximal tension were determined. The results can be summarized as follows: (1) In the absence of macrocycle-1, maximal tension and the maximal and mean rate of tension generation increased with frequency, whereas the time to maximal tension was constant. The rate of decay of tension following maximum tension was greater for 8, 16 and 32 Hz as compared to 1 or 2 Hz. (2) The maximal response to KCl was lower than either FS or carbachol. The maximal rates of tension generation for carbachol and KCl were lower than that of FS; and the rate of tension generation for KCl was lower than that of carbachol. The time to maximal stimulation for KCl was greater than that of either carbachol or FS. (3) Macrocycle-1 had a greater **inhibitory** effect on KCl stimulation than on carbachol stimulation; and a greater **inhibitory** effect on KCl and carbachol stimulation than on FS. (4) The rate of tension generation was more sensitive to macrocycle-1 **inhibition** than was the maximal tension responses to all methods of stimulation. Our current hypothesis is that macrocycle-1 is acting as an intracellular calcium buffer whose affinity constant and association rate does not interfere with rapid intracellular release mechanisms (FS) while it **inhibits** slow intracellular calcium release mechanisms (carbachol and KCl).

L12 ANSWER 29 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97077595 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8920162
TITLE: **Muscarinic** receptor subtypes in the submandibular gland and the **urinary bladder** of the rabbit: in vivo and in vitro functional comparisons of receptor antagonists.
AUTHOR: Tobin G
CORPORATE SOURCE: Department of Physiology and Pharmacology, Goteborg University, Sweden.
SOURCE: Journal of autonomic pharmacology, (1995 Dec) 15 (6) 451-63.
Journal code: 8106455. ISSN: 0144-1795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970108

AB 1. In pentobarbitone anaesthetized rabbits, the **inhibitory** effects of **muscarinic** receptor antagonists with different selectivity profiles were examined on carbachol-evoked submandibular secretion and **urinary bladder** contractions, and on parasympathetically nerve-evoked secretion. On isolated submandibular gland fragments, the **inhibitory** effects of the antagonists were studied on carbachol-evoked release of potassium and on the overflow of tritium in response to electrical field stimulation. 2. In vivo, 4-DAMP equipotently **inhibited** simultaneously carbachol-evoked submandibular secretory and contractile responses of the **urinary bladder**, while pirenzepine was found to be four times as potent in **inhibiting** the secretory response compared with the contractile response. 3. The **inhibition** of carbachol-evoked salivation caused by atropine, 4-DAMP and pirenzepine was as great as their **inhibition** of parasympathetic nerve evoked salivation. Methoctramine exerted less **inhibitory** effect on nerve-evoked salivation than on carbachol-evoked, thus seemingly causing greater presynaptic **inhibition.** 4. In vitro, pirenzepine was only 30 times less potent in **inhibiting** carbachol-evoked potassium release than 4 DAMP (pA2, 9.58 vs 8.10). Whereas atropine, 4 DAMP and pirenzepine abolished the overflow of tritium from isolated glands in response to electrical field stimulation, methoctramine increased it. 5. It is concluded that the **muscarinic** secretory response in the rabbit submandibular gland is exerted via both **muscarinic** M1 and M3 receptors, while the contractile response of the **urinary bladder** to **muscarinic** agonists is exerted via **muscarinic** M3 receptors. The release of acetylcholine from nerve terminals in the gland can be **inhibited** via M2 autoreceptors in rabbits.

L12 ANSWER 30 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97066736 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8910212
TITLE: M1 **muscarinic** receptor-induced facilitation of ACh and noradrenaline release in the rat **bladder** is mediated by protein kinase C.
AUTHOR: Somogyi G T; Tanowitz M; Zernova G; de Groat W C
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh, PA 15261, USA.. somo+@pitt.edu
CONTRACT NUMBER: DK-45741 (NIDDK)
SOURCE: Journal of physiology, (1996 Oct 1) 496 (Pt 1) 245-54.
Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970327
Last Updated on STN: 19970327
Entered Medline: 19970314

AB 1. [3H]Noradrenaline (NA) AND [14C]acetylcholine (ACh) released by electrical field stimulation were measured simultaneously in strips from the body of rat **urinary bladder.** 2. [3H]NA and [14C]ACh release was greater during continuous stimulation (CS; 10 Hz, 100 shocks) or in the presence of eserine than during intermittent train stimulation (IS; 10 Hz, 10 shocks every 5 s, 10 times). Atropine (1 microM) or pirenzepine (0.05-0.1 microM) blocked the CS- or eserine facilitated release. 3. The protein kinase C (PKC) activator phorbol dibutyrate (PDB; 0.05 and 0.5 microM) increased the release of both [3H]NA and [14C]ACh in a concentration dependent manner. Atropine blocked the PDB-induced facilitation of ACh release but not the facilitation of NA release. 4. The protein kinase A (PKA) activator 8 Br-cAMP did not affect ACh **release** but enhanced NA release. 5. The PKC **inhibitor** H-7 (50-100 microM) **inhibited** the CS- or eserine-facilitated release of both ACh and NA, but did not affect the non-facilitated release evoked by IS. H 7 also **inhibited** 0.5 microM PDB-induced facilitation of ACh release but not NA release. 6. Down-regulating PKC by pretreatment for 30 min with 5 microM PDB decreased the facilitated release of ACh and the eserine-induced facilitation of NA release. 7. Electrically evoked contractions of the **bladder** strips exhibited a biphasic response to PDB (2.5 microM), which consisted of an initial enhancement of the peak amplitude and area followed after 20 min by an **inhibition** of contractions. H-7 **inhibited** the electrically evoked contractions in a dose dependent fashion. 8. It is concluded that a phospholipase C-PKC signal transduction pathway is essential for **muscarinic** receptor-induced facilitation of ACh and NA release but is not involved in the non facilitated release of transmitters in the rat **urinary bladder.**

L12 ANSWER 31 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97060766 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8904812
TITLE: Agents for the treatment of overactive detrusor. V. Synthesis and **inhibitory** activity on detrusor contraction of N-tert-butyl-4,4-diphenyl-2-cyclopentenylamine.
AUTHOR: Take K; Okumura K; Tsubaki K; Taniguchi K; Terai T; Shiokawa Y
CORPORATE SOURCE: New Drug Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan.
SOURCE: Chemical & pharmaceutical bulletin, (1996 Oct) 44 (10) 1858-64.
Journal code: 0377775. ISSN: 0009-2363.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961231

AB N-tert-Butyl-4,4-diphenyl-2-cyclopentenylamine ((+/-) 3) was designed to restrict the conformation of terodiline 1 and was synthesized in a 6-step approach starting with diphenylacetaldehyde (10) or in a 4-step approach starting with 2,2-diphenyl-4-pentenoic acid (17). Using di-p-toluoyltartaric acid as a resolving agent, the synthetic (+/-) 3 was resolved into its optically pure forms, (-)- and (+)-3. The (-)-enantiomer (-)-3.HCl (FK584) showed about ten times more potent **inhibitory** activity on **urinary bladder** rhythmic contraction in rats (ED30 = 0.18 mg/kg, i.v.) than terodiline (ED30 = 1.9 mg/kg, i.v.), while the (+)-enantiomer (+)-3.HCl showed no **inhibitory** activity at 1.0 mg/kg i.v. Compound (-)-3.HCl (FK584) has pharmacological properties similar to those of terodiline, as evaluated by in vitro assay and is currently in clinical development for the treatment of overactive detrusor.

L12 ANSWER 32 OF 121 MEDLINE on STN
ACCESSION NUMBER: 97004322 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8851633
TITLE: Effect of thapsigargin on the contractile response of the normal and obstructed rabbit **urinary bladder**.
AUTHOR: Rohrmann D; Zderic S A; Wein A J; Levin R M
CORPORATE SOURCE: Department of Urology, Klinikum der Rheinisch-Westfalischen, Technischen Hochschule, Aachen, Germany.
CONTRACT NUMBER: DK-RO-1-26508 (NIDDK)
DK RO-1-33559 (NIDDK)
DK-RO1-44689 (NIDDK)
SOURCE: Pharmacology, (1996 Feb) 52 (2) 119-24.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961205

AB Excitation-contraction coupling is achieved by translocation of calcium from the extracellular space as well as by the release of calcium from intracellular stores. Thapsigargin has been shown to selectively block the sarcoplasmic Ca-ATPase, thereby preventing the reuptake of calcium into intracellular stores and the participation of these calcium storage sites in the contractile response to stimulation. The current study determined the effect of thapsigargin on the contractile response to field stimulation, bethanechol, and KCl in control rabbit **bladders** and **bladders** obtained from rabbits subjected to partial outlet obstruction. Partial **bladder** outlet obstruction resulted in a marked increase in **bladder** mass and in significant decreases in the contractile response to field stimulation, bethanechol, and KCl. Thapsigargin (5-40 microM) had no effect on the contractile responses of **bladder** strips isolated from control rabbits to field stimulation, bethanechol, or KCl. However, **bladder** strips isolated from obstructed rabbits showed a significant concentration-dependent decrease in the contractile response to field stimulation in the presence of thapsigargin. Thapsigargin had no effect on the contractile responses of **bladder** strips isolated from obstructed rabbits to either bethanechol or KCl. In general, the data described in this study support our current hypothesis: as smooth muscle cells enlarge (hypertrophy) and the cell volume increases, there is an increased dependence on the release of intracellular calcium from the sarcoplasmic reticulum to mediate the contractile response to field stimulation.

L12 ANSWER 33 OF 121 MEDLINE on STN
ACCESSION NUMBER: 96341615 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8750383
TITLE: Urodynamic and other effects of tolterodine: a novel antimuscarinic drug for the treatment of detrusor overactivity.
AUTHOR: Stahl M M; Ekstrom B; Sparf B; Mattiasson A; Andersson K E
CORPORATE SOURCE: Department of Clinical Pharmacology, Lund University Hospital, Sweden.
SOURCE: Neurourology and urodynamics, (1995) 14 (6) 647-55.
Journal code: 8303326. ISSN: 0733 2467.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961025
Last Updated on STN: 19961025
Entered Medline: 19961011

AB Tolterodine, a novel compound intended for treatment of urgency and urge incontinence, has been characterized as a potent **muscarinic** receptor antagonist in pharmacological in vitro and in vivo studies. In cats, tolterodine was shown to reduce **bladder** pressure at doses significantly lower than those affecting salivation. To predict clinical effectiveness, an open pilot study was performed in healthy male volunteers. Efficacy was measured by cystometry and by spontaneously reported effects after administration of a single oral dose of tolterodine, 6.4 mg, given as a water solution. Tolterodine had distinct **inhibitory** effects on **urinary bladder** function, both at 1 and 5 hours post-dose. At 1 hour, but not at 5 hours post-dose tolterodine also significantly reduced stimulated salvation. In addition to the objectively demonstrated changes in urodynamic parameters, most volunteers experienced voiding difficulties. No significant changes in blood pressure, heart rate, or near point of accommodation were registered. Tolterodine, in the dosage used, was both objectively and subjectively shown to exert a marked **inhibitory** effect on micturition in healthy subjects, and the data suggest a more pronounced effect on **bladder** function than on salivation.

L12 ANSWER 34 OF 121 MEDLINE on STN
ACCESSION NUMBER: 96218053 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8641667
TITLE: Toxicological comparison of a **muscarinic** agonist given to rats by gavage or in the diet.
AUTHOR: Dethloff L A; Chang T; Courtney C L
CORPORATE SOURCE: Department of Pathology, Parke-Davis Pharmaceutical Research, Ann Arbor, MI 48105, USA.
SOURCE: Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, (1996 Apr) 34 (4) 407-22.
Journal code: 8207483. ISSN: 0278 6915.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 19960726
Entered Medline: 19960717

AB Corneal opacities and **urinary** tract sepsis were previously observed by the authors in rats given **muscarinic** agonists mixed in the diet or by gavage. To explain the differential toxicity generated by each means of administration, toxicokinetics of the **muscarinic** agonist CI-979 were investigated. In addition, the **muscarinic** antagonist scopolamine was co-administered with CI-979 to evaluate the relationship of these effects to pharmacological mechanism of action of CI-979. Female rats were given CI-979 daily by gavage at 0, 1, 10 and 30 mg/kg body weight or in the diet at 0, 1, 10 and 50 mg/kg body weight for up to 14 days. Dose-related clinical signs of **muscarinic** stimulation, such as sialorrhoea and dacryorrhoea, were observed predominantly in rats given 10 and 30 mg/kg body weight CI 979 by gavage, and corresponded with the high plasma drug concentrations. In contrast, hydronephrosis, pyelonephritis, and inflammation and necrosis of the kidney, **urinary bladder**, urethra and **urinary** papilla were linked to sustained, albeit lower plasma drug concentrations attained by dietary administration of CI-979 at 10 and 50 mg/kg body weight. Comparable incidences of corneal opacities were induced by both means of administration, but lesions appeared more rapidly and were generally of greater severity when CI-979 was given in the diet. The induction of corneal lesions, as well as **urinary** sepsis, may not relate simply to maximum plasma concentrations or to areas under the curve per se, but rather may arise when plasma drug concentrations are sustained. Corneal opacification and development of **urinary** tract pathology were **inhibited** by scopolamine, suggesting that these effects were related to the **muscarinic** mechanism of action of CI-979.

L12 ANSWER 35 OF 121 MEDLINE on STN
ACCESSION NUMBER: 96162560 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8583354
TITLE: Analysis of the mechanisms underlying the contractile response induced by the hydroalcoholic extract of Phyllanthus urinaria in the guinea-pig **urinary bladder** in-vitro.
AUTHOR: Dias M A; Campos A H; Cechinel Filho V; Yunes R A; Calixto J B
CORPORATE SOURCE: Department of Pharmacology, Universidade Federal de Santa Catarina, Florianopolis SC, Brazil.
SOURCE: Journal of pharmacy and pharmacology, (1995 Oct) 47 (10) 846-51.
Journal code: 0376363. ISSN: 0022-3573.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960327
Last Updated on STN: 19980206
Entered Medline: 19960315

AB The hydroalcoholic extract of Phyllanthus urinaria (Euphorbiaceae), substance P and substance P methyl ester all caused graded contractions in the guinea-pig **urinary bladder**. Responses to hydroalcoholic extract and substance P were markedly **inhibited** in calcium-free Krebs solution, this effect being reversed by reintroduction of calcium in the medium. The contraction in response to hydroalcoholic extract was unaffected by atropine, propranolol, prazosin, yohimbine, tetrodotoxin, w conotoxin, nicardipine, HOE 140, guanethidine, staurosporine, phorbol ester or indomethacin, excluding the involvement of nervous mediated responses, or action via cholinergic, adrenergic, kinins, cyclo-oxygenase metabolites, protein kinase C or activation of L or N-type calcium channels. The selective NK1 tachykinin antagonist (FK 888), but not NK2 (SR 48968) antagonized substance P-induced contraction, but both drugs failed to effect Phyllanthus urinaria-induced contraction. Prolonged desensitization of guinea pig **urinary bladder** with capsaicin (10 microM) or preincubation of guinea-pig **urinary bladder** with capsazepine did not affect contraction caused by hydroalcoholic extract. Ruthenium red almost completely abolished capsaicin-induced contraction, but had no effect on hydroalcoholic extract-mediated contraction. Substance P and the hydroalcoholic extract caused marked potentiation of the twitch response in the preparations field stimulated. The facilitatory effect of substance P, but not that of hydroalcoholic extract, was prevented by the NK1 (FK 888), but not by NK2 (SR 48968) antagonist. We concluded that contraction induced by hydroalcoholic extract of Phyllanthus urinaria in the guinea pig **urinary bladder** involves direct action on smooth muscle and relies on the mobilization of extracellular calcium influx unrelated to activation of L- and N type calcium channels or activation of protein kinase C mechanisms. In addition contraction caused by the hydroalcoholic extract of Phyllanthus urinaria in guinea-pig **urinary bladder** does not involve the activation of tachykinin or vanilloid receptors.

L12 ANSWER 36 OF 121 MEDLINE on STN
ACCESSION NUMBER: 96160127 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8588301
TITLE: A review of nonpesticide phosphate ester-induced neurotoxicity in cattle.
AUTHOR: Coppock R W; Mostrom M S; Khan A A; Stair E L
CORPORATE SOURCE: Environmental Toxicology Research, Alberta Environmental Centre, Vegreville, Canada.
SOURCE: Veterinary and human toxicology, (1995 Dec) 37 (6) 576-9. Ref: 20
Journal code: 7704194. ISSN: 0145-6296.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960404
Last Updated on STN: 19960404
Entered Medline: 19960327

AB Nonpesticide phosphate esters induce delayed neurotoxicity in cattle. The most common exposures are to complex mixtures of triaryl phosphate used in lubricating oils. Oral ingestion is most common, but dermal exposures have also occurred. Clinical signs of **cholinesterase** (ChE) **inhibition** may or may not be seen. Depending on the biochemical targets, the percent reduction in blood ChE is variable and can be < 30% of normal activity. Organophosphate ester-induced delayed neurotoxicity cannot be predicted by **inhibition** of blood ChEs. Signs of delayed neurotoxicity occur 2 to 25 d after exposure; these signs are neurologic deficiencies of the antigravity muscles and the muscles of the **urinary bladder** and larynx. Affected cattle may dribble urine and some may be mute. Signs of ChE **inhibition** generally are not observed in animals with neurological deficiencies. Pathologic findigs are axonopathy and myelin degeneration of nerves with long axons located in both the peripheral and central nervous systems. In the spinal cord, location of the affected nerve tracts is variable. Degenerative changes occur in motor neurons. Calves are less susceptible to organophosphate ester-induced delayed neurotoxicity than cows. A dose of 500 mg triaryl phosphate/kg body weight will produce complete paralysis in a mature cow in 26 d.

L12 ANSWER 37 OF 121 MEDLINE on STN
ACCESSION NUMBER: 96073411 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7576597
TITLE: **Muscarinic** suppression of Ca2+ current in smooth muscle cells of the guinea-pig **urinary bladder.**
AUTHOR: Yoshino M; Yabu H
CORPORATE SOURCE: Department of Physiology, Sapporo Medical University, Japan.
SOURCE: Experimental physiology, (1995 Jul) 80 (4) 575-87.
Journal code: 9002940. ISSN: 0958-0670.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 20000303
Entered Medline: 19951205

AB The suppressive action of carbachol (CCh) on the Ca2+ current (ICa) in smooth muscle cells of the guinea pig **urinary bladder** was investigated using the whole-cell patch clamp technique. Bath application of 10 microM CCh reduced the amplitude of ICa by 92 +/- 3.8% (n = 9). Adding 1 microM atropine to the bath completely blocked the action of CCh, indicating that the suppressive action of CCh on ICa is mediated by the activation of **muscarinic** receptors. Intracellular perfusion of the non-hydrolysable GTP analogue, guanosine 5'-O-(3-thiotriphosphate) (GTP gamma S; 200 microM) mimicked the effects of CCh. Sustained suppression of ICa was observed when GTP gamma S was present in the cytoplasm. Intracellular perfusion of inositol 1,4,5-trisphosphate (InsP 3; 20 microM) also suppressed ICa; its effect was not sustained but transient. The protein kinase C activator, phorbol 12,13-dibutyrate (PDBu), however, could not mimic the effects of CCh on ICa. When intracellular Ca2+ was strongly buffered by the Ca2+ chelator EGTA (20 mM) in the patch pipette, the sustained suppression of ICa was abolished. Inclusion of 3 mg/ml heparin, a blocker of InsP3-induced Ca2+ release, in the patch pipette reduced the degree of sustained ICa suppression by 43.2 +/- 1.9% (n = 7). Adding thapsigargin (TG), a sarcoplasmic reticulum Ca2+-ATPase **inhibitor**, to a wash solution reduced the recovery of ICa by about 50%, suggesting that approximately half of the ICa suppression induced by CCh is due to Ca2+ release from TG-sensitive internal Ca2+ stores. From these results it appears that CCh suppresses ICa via two independent mechanisms: (1) Ca(2+) mediated inactivation of the Ca2+ channel, which is caused by Ca2+ release from InsP3- and TG sensitive internal stores, and (2) a GTP-binding protein-mediated mechanism, which requires intracellular Ca2+.

L12 ANSWER 38 OF 121 MEDLINE on STN
ACCESSION NUMBER: 96022482 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7580750
TITLE: [The role of protein kinase C and **muscarinic** cholinoreceptors in vasopressin-stimulated water transport].
O roli proteinkinazy C i muskarinovykh kholinoretseptorov v stimulirovannom vazopressinom vodnom transporte.
AUTHOR: Bagrov Ia Iu; Dmitrieva N I; Manusova N B
SOURCE: Eksperimental'naia i klinicheskaia farmakologiia, (1995 Jul-Aug) 58 (4) 33-5.
Journal code: 9215981. ISSN: 0869-2092.
PUB. COUNTRY: RUSSIA: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951213

AB The role of protein kinase C (PKC) in the control of vasopressin-stimulated water transport in the frog **urinary bladder** and its modulation by M2-agonist oxotremorine has been studied. Using the PKC **inhibitor**, staurosporine we showed that PKC in the region pf the basal membrane suppressed vasopressin-stimulated water transport, whereas PKC in the apical region potentiated this transport. It was also found that from the two types of oxotremorine action on stimulated water transport determined by its concentration only **inhibition** is mediated through PKC.

L12 ANSWER 39 OF 121 MEDLINE on STN
ACCESSION NUMBER: 96007972 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8566107
TITLE: In vivo and in vitro effects of **muscarinic** receptor antagonists on contractions and release of [3H]acetylcholine in the rabbit **urinary bladder.**
AUTHOR: Tobin G; Sjogren C
CORPORATE SOURCE: Department of Pharmacology, University of Goteborg, Sweden.
SOURCE: European journal of pharmacology, (1995 Jul 25) 281 (1) 1-8.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960306

AB The functional effects of **muscarinic** receptor antagonists were examined in vivo and in vitro on the rabbit **urinary bladder. Inhibitory** effects on carbachol-evoked contractions of detrusor strips were pronounced for 4-diphenylacetoxy-N-methylpiperidine (4-DAMP; -logIC50: 8.64), p-fluoro-hexahydro-sila-diphenidol (pFHHSiD; 7.84) and atropine (8.27), while they were less pronounced for pirenzepine (6.62) and methoctramine (5.36). 4-DAMP and methoctramine increased 3H overflow from [3H]choline-labelled strips in response to electrical stimulation, contrary to pirenzepine, which decreased the overflow. Concomitant contractions were markedly reduced by 4-DAMP and by pirenzepine, but not by methoctramine. The -logIC50 estimations for atropine-sensitive electrically evoked contractions revealed methoctramine (4.85) to be less potent on nerve evoked contractions than on carbachol-evoked contractions, in contrast to pirenzepine (7.15) and 4-DAMP (9.15). The effects of the antagonists in anaesthetized rabbits resembled those in vitro. Thus, **muscarinic** receptors in the rabbit **urinary bladder** are heterogeneous; prejunctional facilitatory (M1) and **inhibitory** (M2) for acetylcholine release, and postjunctional **muscarinic** M3 receptors mediating contractile responses.

L12 ANSWER 40 OF 121 MEDLINE on STN
ACCESSION NUMBER: 95203909 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7896306
TITLE: Effects of adenosine on contractility and 45Ca-uptake in rat **urinary bladder**.
AUTHOR: Parija S C; Raviprakash V; Mishra S K
CORPORATE SOURCE: Division of Pharmacology and Toxicology, Indian Veterinary Research Institute, Izatnagar.
SOURCE: Indian journal of experimental biology, (1994 Nov) 32 (11) 781-5.
Journal code: 0233411. ISSN: 0019-5189.
PUB. COUNTRY: India
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950504
Last Updated on STN: 19950504
Entered Medline: 19950425

AB Effects of adenosine on K+ and ACh-stimulated contractility and 45Ca uptake were studied in the rat **urinary bladder** smooth muscle and were compared with those of nifedipine. Both adenosine (10(-5) M) and nifedipine (10(-7) M/10(-8) M) significantly **inhibited** the contractions elicited by K+ (10(2)-32 x 10(-2) M), Ca2+ (10(-4)-3 x 10(-2 M) in K(+) depolarized preparations and ACh (10(-9) M-3 x 10(-3) M). Further, adenosine (10(-5) M) significantly (P < 0.05) **inhibited** K+ (10(-1) M)-stimulated 45Ca uptake in the **bladder** strips. However, it had little effect on inward 45Ca movement resulting from ACh (10(-4) M)-induced stimulation. On the other hand, nifedipine (10(-7) M) significantly (P < 0.001) reduced both K+ and ACh-induced 45Ca-uptake in this tissue. It is concluded that the calcium channel blocking action of adenosine is limited to Ca2+ uptake through voltage operated calcium channels, while receptor operated calcium channels activated by **muscarinic** receptor stimulation appear to be insensitive to the purine.

L12 ANSWER 41 OF 121 MEDLINE on STN
ACCESSION NUMBER: 95156307 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7853228
TITLE: M1 **muscarinic** receptor-mediated facilitation of acetylcholine release in the rat **urinary bladder**.
AUTHOR: Somogyi G T; Tanowitz M; de Groat W C
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh, PA 15261.
CONTRACT NUMBER: MH 30915 (NIMH)
SOURCE: Journal of physiology, (1994 Oct 1) 480 (Pt 1) 81-9.
Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19950322
Entered Medline: 19950310

AB 1. Release of [3H]ACh in response to electrical field stimulation (10 Hz) was measured in strips of rat **urinary bladder** and cardiac atrial tissues previously incubated with [3H]choline. 2. The volley output of [3H]ACh release was positively correlated with frequency of stimulation in the **urinary bladder** but negatively correlated in the atrium. 3. The quantity of [3H]ACh release was influenced by the pattern and duration of stimulation. Continuous stimulation (CS) with trains of 100 shocks released 10 times larger amounts of ACh than the same number of shocks presented as short trains of intermittent stimulation (IS): ten shocks per train with 5 s inter-train intervals. 4. The facilitation of transmitter release was antagonized completely by the administration of atropine (1 microM) or pirenzepine (0.05 microM), a selective M1 antagonist. Eserine, an anticholinesterase agent, markedly facilitated ACh release induced by CS and IS. This effect was blocked by atropine. 5. Release of ACh from atrial strips did not exhibit CS induced facilitation. Eserine decreased IS- and CS-evoked ACh release in the atrium. 6. It is concluded that continuous stimulation of postganglionic cholinergic nerves in the rat **urinary bladder** leads to the activation of M1 **muscarinic**, facilitatory presynaptic receptors which enhance the release of ACh. Presynaptic facilitation may be an important mechanism for modulating neural input to the **bladder** during micturition.

L12 ANSWER 42 OF 121 MEDLINE on STN
ACCESSION NUMBER: 95151079 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7848339
TITLE: **Urinary bladder**-selective action of the new antimuscarinic compound vamicamide.
AUTHOR: Oyasu H; Yamamoto T; Sato N; Sawada T; Ozaki R; Mukai T; Ozaki T; Nishii M; Sato H; Fujiwara T; +
CORPORATE SOURCE: Pharmacological Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan.
SOURCE: Arzneimittel-Forschung, (1994 Nov) 44 (11) 1242-9.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950316
Last Updated on STN: 19950316
Entered Medline: 19950306

AB 1. The **inhibitory** action of vamicamide (FK176, (+/-)-(2R*,4R*)-4-dimethylamino-2-phenyl-2-(2 pyridyl)valeramide, CAS 132373-81-0) on the responses of various tissues to the cholinergic agonists, carbachol and McN-A-343 (4-[m-chlorophenylcarbamoyloxy]-2-butynyl-trimethylammonium chloride, CAS 55-45 8), was investigated in isolated tissue preparations. Vamicamide showed competitive antagonistic actions against all the preparations tested and its pA2 value for the **urinary bladder** was 6.82, which was higher than that for the atria (5.94) and almost the same as that for the vas deferens (6.90) and for the stomach (6.81). The pA2 values of oxybutynin hydrochloride (oxybutynin) and atropine sulfate monohydrate (atropine) were nearly the same in all the tissues tested. 2. Oral administration of vamicamide 0.11-1.0 mg/kg **inhibited** dose-dependently spontaneous **bladder** contractions caused by raising the intravesical volume in conscious rats. **Inhibitory** actions were also obtained with 0.32-3.2 mg/kg of oxybutynin or 0.0032-0.032 mg/kg of atropine, but the duration of action of oxybutynin was shorter than that of vamicamide or atropine. Vamicamide further **inhibited bladder** contractions in rats following intravesical administration of 0.05-0.5 mg/ml solution. 3. Vamicamide had no effect or only slightly **inhibited** spontaneous motility of the stomach and distal colon in conscious rats, as well as heart rate and salivary secretion in conscious dogs, after oral dosing with 3.2 mg/kg of the compound. Similar results were obtained with oxybutynin, excepting the occurrence of tachycardia. (ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 43 OF 121 MEDLINE on STN
ACCESSION NUMBER: 95147990 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7845476
TITLE: The role of extracellular Ca2+ in carbachol induced tonic contraction of the pig detrusor smooth muscle.
AUTHOR: Uchida W; Masuda N; Shirai Y; Shibasaki K; Satoh N; Takenada T
CORPORATE SOURCE: Cardiovascular and Atherosclerosis Research Laboratories, Yamanouchi Institute for Drug Discovery Research, Ibaraki, Japan.
SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (1994 Oct) 350 (4) 398-402.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950316
Last Updated on STN: 19950316
Entered Medline: 19950307

AB The role of extracellular Ca2+ in the tonic-contractile response to **muscarinic** receptor stimulation was investigated in isolated detrusor smooth muscle from the pig **urinary bladder.** Carbachol (10(8)-10(-5) M) produced a concentration-dependent contractile response in isolated pig detrusor smooth muscle strips consisting of an initial phasic component followed by a tonic component. During the plateau of the tonic contractions induced by carbachol at the submaximal concentration of 10(-6) M, the **inhibiting** effects of atropine, EGTA, nifedipine (a voltage-dependent calcium channel antagonist), H-7 [a protein kinase C (PKC) **inhibitor**] and YM934 (a potassium channel opener) on the contractions were evaluated. Atropine (10(-10)-3 x 10(-8) M) concentration-dependently **inhibited** the tonic contractions induced by carbachol. In the same experimental conditions, EGTA (4 mM) and nifedipine (10(-9)-3 x 10(-7) M) depressed the tonic contractions in a concentration-dependent manner as did H-7 (10(-5)-3 x 10(-5) M) and YM934 (10(-8)-10(6) M). However, H-7 (10(5)-3 x 10(-5) M) and YM934 (10(-6) M) were very weak in **inhibiting** the contractions induced by KCl (50 mM) in isolated pig detrusor smooth muscle strips. These results suggest that the tonic-contractile response induced by carbachol in pig detrusor smooth muscle strips is dependent mainly on depolarization of the cell membranes and an influx of extracellular Ca2+, and also suggest that this depolarizing response may be due to inactivation of ATP-sensitive potassium channels through **muscarinic** activation of PKC.

L12 ANSWER 44 OF 121 MEDLINE on STN
ACCESSION NUMBER: 94287486 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8016895
TITLE: **Muscarinic** acetylcholine receptor subtypes in smooth muscle.
COMMENT: Comment on: Ugeskr Laeger. 1993 Aug 9;155(32):2438-42. PubMed ID: 8102824
Comment in: Trends Pharmacol Sci. 1994 Nov;15(11):407-8. PubMed ID: 7855902
AUTHOR: Eglen R M; Reddy H; Watson N; Challiss R A
CORPORATE SOURCE: Institute of Pharmacology, Syntex Discovery Research, Palo Alto, CA 94304.
SOURCE: Trends in pharmacological sciences, (1994 Apr) 15 (4) 114-9. Ref: 50
Journal code: 7906158. ISSN: 0165-6147.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Commentary
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940810
Last Updated on STN: 20000303
Entered Medline: 19940728

AB **Muscarinic** acetylcholine M2 and M3 receptor subtypes are coexpressed in many types of smooth muscle including gastrointestinal smooth muscle, **urinary bladder** and vascular and airway tissue. Activation of M3 receptors, via the G protein Gq, results in increased polyphosphoinositide hydrolysis, release of Ca2+ ions from the sarcoplasmic reticulum and consequently causes contraction. Quantitation of the relative expression of M2 and M3 receptors has shown that the proportion of M2 receptors often predominates over the M3 receptor population by 4:1 or more. Although it is established that M2 receptors preferentially link, via a pertussis-toxin-sensitive G protein Gi, to **inhibition** of adenylate cyclase activity, relatively little is known concerning the physiological role of the M2 receptor population. In this review, Richard Eglen and colleagues discuss recent data concerning the possible role(s) of **muscarinic** receptor subtypes in smooth muscle and appraise the pharmacological methods for dissecting the function of **muscarinic** receptor subtypes in tissues co expressing multiple receptors.

L12 ANSWER 45 OF 121 MEDLINE on STN
ACCESSION NUMBER: 94181045 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8133908
TITLE: **Inhibitory** effects of propiverine on rat and guinea-pig **urinary bladder** muscle.
AUTHOR: Tokuno H; Chowdhury J U; Tomita T
CORPORATE SOURCE: Department of Physiology, School of Medicine, Nagoya University, Japan.
SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (1993 Dec) 348 (6) 659-62.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940428
Last Updated on STN: 19940428
Entered Medline: 19940420

AB In muscle strips isolated from guinea-pig and rat **urinary bladder**, propiverine (3-10 microM) **inhibited** carbachol-induced contractions in the presence of verapamil and Ca(2+)-induced contractions in excess K+ medium containing atropine, suggesting it has both anticholinergic and Ca2+ channel blocking actions. The Ca2+ channel blocking action was also demonstrated by recording inward Ca2+ currents in single cells dispersed from both species. The **inhibition** of inward currents by propiverine was three times stronger in the rat than the guinea-pig, ID50 being 7 microM for rat and 21 microM for guinea-pig. The recovery of the current after washout was faster than that of mechanical **inhibition**. It is concluded that propiverine blocks not only **muscarinic** receptors, but also Ca2+ channels at similar concentrations.

L12 ANSWER 46 OF 121 MEDLINE on STN
ACCESSION NUMBER: 94106595 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8279533
TITLE: **Muscarinic inhibition** of ATP-sensitive K+ channels by protein kinase C in **urinary bladder** smooth muscle.
AUTHOR: Bonev A D; Nelson M T
CORPORATE SOURCE: Department of Pharmacology, University of Vermont, Colchester 05446-2500.
CONTRACT NUMBER: HL-44455 (NHLBI)
SOURCE: American journal of physiology, (1993 Dec) 265 (6 Pt 1) C1723-8.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 19940218
Last Updated on STN: 20021219
Entered Medline: 19940208

AB We explored the possibility that **muscarinic** receptor stimulation can **inhibit** ATP-sensitive K+ (KATP) channels in smooth muscle cells from guinea pig **urinary bladder**. Whole cell K+ currents were measured in smooth muscle cells isolated from the detrusor muscle of the guinea pig **bladder**. Stimulation of **muscarinic** receptors by carbachol (CCh; 10 microM) **inhibited** KATP currents by 60.7%. Guanosine 5'-O-(2-thiodiphosphate) in the pipette (internal) solution prevented the CCh-induced **inhibition** of KATP currents. Activators of protein kinase C (PKC), a diacylglycerol analogue, and phorbol 12-myristate 13-acetate **inhibited** KATP currents by 63.5 and 73.9%, respectively. Blockers of PKC (bisindolylmaleimide GF-109203X and calphostin C) greatly reduced CCh **inhibition** of KATP currents. We propose that **muscarinic** receptor stimulation **inhibits** KATP channels in smooth muscle cells from **urinary bladder** through activation of PKC.

L12 ANSWER 47 OF 121 MEDLINE on STN
ACCESSION NUMBER: 94035894 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8106107
TITLE: Effects of excitatory neurotransmitters on Ca2+ channel current in smooth muscle cells isolated from guinea-pig **urinary bladder.**
AUTHOR: Nakayama S
CORPORATE SOURCE: University Department of Pharmacology, Oxford.
SOURCE: British journal of pharmacology, (1993 Sep) 110 (1) 317-25.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19950206
Entered Medline: 19931214

AB 1. A whole-cell voltage clamp technique was used to examine the effects of purinoceptor and **muscarinic** receptor agonists on voltage-sensitive Ca2+ channels in guinea-pig isolated **urinary bladder** cells. 2. When the cell membrane was clamped at the holding potential, rapid application of ATP elicited a large inward current in normal solution containing 2.5 mM Ca2+, and reduced the subsequent Ca2+ channel current evoked by a depolarizing pulse (0 mV). Carbachol (CCh) elicited little membrane current, but similarly reduced the Ca2+ current. 3. When purinoceptor agonists were rapidly applied during conditioning depolarizations at +80 mV, an outward current was elicited, and the Ca2+ channel current evoked by the subsequent test potential of 0 mV was not affected. Application of CCh at +80 mV also elicited an outward current, but it reduced the subsequently evoked Ca2+ current. 4. The **inhibitory** effect of **muscarinic** agonists on the Ca2+ channel current was attenuated by caffeine (10 mM). 5. In Ca(2+)-free, low Mg2+ solution, a Na+ current flowing through voltage-dependent Ca2+ channels was evoked by depolarization. This current was not reduced by bath application of purinoceptor agonists (ATP and alpha,beta-methylene ATP). 6. These results suggest that the main effect of purinoceptor stimulation is opening of non-selective cation channels, and that **muscarinic** stimulation triggers Ca2+ release from intracellular stores. Voltage-sensitive Ca2+ channels are inactivated through an increase in intracellular Ca2+ induced by either activation of purinoceptor or **muscarinic** receptors.

L12 ANSWER 48 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93374286 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8365654
TITLE: Role of calcium in mediating the biphasic contraction of the rabbit **urinary bladder**.
AUTHOR: Zhao Y; Wein A J; Levin R M
CORPORATE SOURCE: Division of Urology, University of Pennsylvania School of Medicine, Philadelphia 19104.
CONTRACT NUMBER: P50-DK-39257 (NIDDK)
RO-1-DK 26508 (NIDDK)
RO-1-DK133559 (NIDDK)
SOURCE: General pharmacology, (1993 May) 24 (3) 727-31.
Journal code: 7602417. ISSN: 0306-3623.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931022
Last Updated on STN: 19931022
Entered Medline: 19931001

AB 1. The response of the **urinary bladder** to field stimulation is biphasic in nature consisting of an initial phasic contraction followed by a prolonged tonic phase which lasts for the duration of the stimulation. 2. The phasic response is mediated by the release of neurohumoral transmitters, primarily acetylcholine (via **muscarinic** receptor stimulation) and ATP (via purinergic receptor stimulation). The tonic component is mediated entirely via **muscarinic** receptor stimulation. 3. The present study investigates the dependence on extracellular calcium of the phasic and tonic contractile responses to field stimulation, bethanechol, and ATP. The results can be summarized as follows: 4. Field stimulation (2 and 32 Hz) and bethanechol evoke a biphasic contractile response whereas ATP evokes only a phasic response. 5. There were no significant effects of either calcium channel blockers or calcium fee EGTA medium on either spontaneous contraction or basal tension of muscle strips. 6. The calcium channel antagonists diltiazem and verapamil **inhibited** both the phasic and tonic responses induced by field stimulation (both 2 and 32 Hz) in a dose dependent manner. 7. For both 2 and 32 Hz stimulation, the ED50 s for the **inhibition** of the tonic phases of the responses to field stimulation were significantly lower than the ED50s for the **inhibition** of the phasic responses. 8. The tonic phase of the responses to field stimulation were **inhibited** to a significantly greater degree than the phasic responses by incubation in calcium-free medium containing EGTA. 9. Both the phasic and tonic components of the response to bethanechol stimulation were **inhibited** equally, and followed a similar time course as the tonic component of field stimulation.(ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 49 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93251320 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8485622
TITLE: Differential changes of adrenoceptor- and **muscarinic** receptor-linked prostacyclin synthesis by the aorta and **urinary bladder** of the diabetic rat.
AUTHOR: Jeremy J Y; Thompson C S; Mikhailidis D P
CORPORATE SOURCE: Department of Chemical Pathology and Human Metabolism, Royal Free Hospital and School of Medicine, University of London.
SOURCE: British journal of pharmacology, (1993 Apr) 108 (4) 1131-6.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19970203
Entered Medline: 19930604

AB 1. The effect of experimental diabetes mellitus (DM; hyperglycaemic, non-ketototic; 2 months duration) in the rat on receptor-linked prostacyclin (PGI2) synthesis (measured as 6-oxo-PGF1 alpha by radioimmunoassay) was studied in the aorta and **urinary bladder** using adrenaline, angiotensin II (AII) and acetylcholine (ACh). Signal transduction systems were studied via stimulation of PGI2 synthesis with phorbol ester dibutyrate (PDBU; a protein kinase C activator [PKC]), Ca2+ ionophore A23187 (A23187) and thapsigargin (both elevate intracellular Ca2+, activating phospholipase A2 [PLA2]) and arachidonate (AA; substrate for PGI2 synthesis). 2. In response to adrenaline, AII and phorbol ester, aortic PGI2 release was markedly reduced (all > 75%) in diabetic rats compared to controls. EC50s of the dose-response curves for adrenaline, AII and PDBU were also markedly increased in aortae from DM rats compared to controls. Although there was decreased output of PGI2 in response to A23187 by aortae from diabetic rats compared to controls, there was no difference in the EC50s (mean +/- s.e. mean: diabetic, 2.7 +/ 0.2 x 10(-6) M; controls 2 +/- 0.18 x 10(-6) M). There were no differences in PGI2 release (or in the EC50s) in response to thapsigargin or AA between aortae from diabetic and control rats. 3. In the **urinary bladder**, there was a marked increase in PGI2 output in response to ACh and a marked decrease in EC50s for the ACh-PGI2 dose-response curves in diabetic rats (EC50 = 5.8 +/- 0.32 x 10(7) M) compared to controls (EC50 = 2.2 +/ 0.15 x 10(-6) M).(ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 50 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93247153 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8387115
TITLE: The pathophysiology of contractile activity in the chronic decentralized feline **bladder**.
AUTHOR: Skehan A M; Downie J W; Awad S A
CORPORATE SOURCE: Department of Urology, Dalhousie University, Halifax, Nova Scotia, Canada.
SOURCE: Journal of urology, (1993 May) 149 (5) 1156-64.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19930618
Entered Medline: 19930528

AB Autonomous wave activity occurs in the decentralized **bladder** and may contribute to upper tract damage and incontinence. In order to clarify the poorly understood pathophysiology and neuropharmacology of autonomous waves, cats were prepared with L7-S3 ventrodorsal rhizotomy alone or with L7-S3 ventral rhizotomy with and without total sympathectomy. The incidence of autonomous waves was < 15% 12 weeks after ventral or ventrodorsal rhizotomy, but acute sympathectomy at 13 weeks increased the incidence to 58% in these groups. With chronic sympathectomy the incidence was 100%. This suggests that the waves arise locally via a mechanism which is independent of L7 S3 dorsal roots, due to lack of a suppressive sympathetic pathway. Autonomous waves were **inhibited** by atropine after acute sympathectomy and by prazosin after chronic sympathectomy, but increased **inhibition** occurred after both drugs in either case. Adrenergic neuron depletion with 6-hydroxydopamine enhanced wave activity, which was incompletely **inhibited** by subsequent atropine. This implies that the peripheral reflex pathway has facilitatory alpha 1-adrenergic, **muscarinic** and also noncholinergic nonadrenergic elements. Clinically, sensory or sympathetic damage caused incontinence, but sympathectomy also caused high pressure waves, which may cause upper tract damage and treatment resistant incontinence in patients.

L12 ANSWER 51 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93207573 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8384453
TITLE: Effects of terflavoxate on stimulated contractions of **urinary bladder** in vitro.
AUTHOR: Testa R; Guarneri L; Bernasconi P; Angelico P; Ibba M; Poggesi E; Meli A
CORPORATE SOURCE: Pharmacology Laboratories, Recordati S.p.A., Milan, Italy.
SOURCE: Arzneimittel-Forschung, (1993 Feb) 43 (2) 122-8.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930507
Last Updated on STN: 19930507
Entered Medline: 19930422

AB The antispasmodic activity of terflavoxate (CAS 86433-39-8), a flavone derivative with spasmolytic properties on the **urinary** tract, has been studied in vitro, in comparison to the most common drugs utilized in the therapy of overactive detrusor, namely flavoxate, oxybutynin, and terodiline. Terflavoxate showed affinity for **bladder** (and brain) **muscarinic** receptors at micromolar level, however, its activity on carbachol-induced contractions of rat **bladder** was clearly non competitive, indicating that the compound is devoid of functional antimuscarinic property. Moreover, the observation that unlike antimuscarinic drugs, terflavoxate **inhibited** by more than 50% field stimulation-induced contractions of rabbit **bladder** strips, indicates that mechanisms other than the anticholinergic one should be responsible for its smooth muscle relaxant properties. Terflavoxate, flavoxate, oxybutynin, and terodiline were equally effective in **inhibiting** the two components of K(+)-induced contractions, while nifedipine and nicardipine were more potent than the other compounds, and more effective in **inhibiting** tonic than phasic contractions. In addition, while nifedipine and nicardipine antagonized in a competitive manner calcium-induced contractions of potassium-depolarized **bladder** strips, the other spasmolytics behaved as mixed antagonists. Differences in calcium antagonistic properties between nifedipine and nicardipine on one side, and terflavoxate on the other, are further demonstrated by the data on binding experiments. Nevertheless, present results suggest that Ca(++)-antagonistic effects are mainly responsible for terflavoxate smooth muscle relaxant properties.

L12 ANSWER 52 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93113409 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1282072
TITLE: A pharmacological study of NK1 and NK2 tachykinin receptor characteristics in the rat isolated **urinary bladder.**
AUTHOR: Hall J M; Flowers J M; Morton I K
CORPORATE SOURCE: Pharmacology Group, King's College London, London.
SOURCE: British journal of pharmacology, (1992 Nov) 107 (3) 777-84. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930219
Last Updated on STN: 19960129
Entered Medline: 19930202

AB 1. We have estimated potencies of tachykinin receptor agonist and antagonist analogues in order to determine the recognition characteristics of tachykinin receptors mediating phasic contractile responses of the rat isolated **urinary bladder** in vitro. 2. The NK1-selective synthetic agonists, substance P methyl ester and GR73632, the synthetic NK2-selective agonists [beta-Ala8]-NKA(4-10) and GR64349, and the mammalian tachykinins, neurokinin A and neurokinin B, were assayed relative to substance P and were found to be approximately equipotent. The NK3-selective agonist, senktide, was inactive (10 microM). 3. Potencies of all these agonists were not significantly different (P > 0.05) when experiments were carried out in the presence of the neutral endopeptidase **inhibitor**, phosphoramidon, and the kininase II **inhibitor**, enalaprilat (both 1 microM). 4. The NK1-selective antagonist, GR82334, **inhibited** responses to substance P methyl ester in a competitive manner in the rat **urinary bladder** and the rat ileum, and also in the guinea-pig ileum. Markedly different pKB estimates were obtained in the rat **bladder** (6.38) and rat ileum (6.56) compared to the guinea-pig ileum (7.42). GR82334 (3 microM) was inactive against responses of the rat **bladder** to [beta-Ala8]-NKA(4-10). 5. The NK1-selective antagonist (+/-)-CP 96,345 also **inhibited** responses of the rat **bladder** and guinea-pig ileum to substance P methyl ester; however, in the rat **bladder** at 1 microM, this antagonist reversibly **inhibited** responses both to the NK2 selective agonist [beta Ala8] NKA(4-10) and to the **muscarinic** agonist carbachol (P < or = 0.01), thus showing evidence of some non-selective depressant actions. (ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 53 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93103664 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1281645
TITLE: Possible regulatory role of dynorphin A in the **urinary bladder.**
AUTHOR: Berggren A; Dahlstrom A; Rubenson A; Sillen U
CORPORATE SOURCE: Department of Pediatric Surgery, Ostra Hospital, Gothenburg, Sweden.
SOURCE: Journal of neural transmission. General section, (1992) 90 (1) 33-44. Journal code: 9002201. ISSN: 0300-9564.
PUB. COUNTRY: Austria
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930212
Last Updated on STN: 19960129
Entered Medline: 19930127

AB Muscle strips from rat and human detrusor were studied using indirect immunofluorescence and electrical nerve stimulation in an organ bath. Immunoreactivity towards dynorphin was observed in varicose nerve fibres in the detrusor muscle and around immunonegative nerve cell bodies in the prevesical ganglia of the rat. In vitro, dynorphin A (1-13) (10(-13)-10(-6) M) strongly facilitated detrusor contraction induced by electrical field stimulation (EFS). This facilitation was counteracted by morphine (10(10) and 10(-8) M) and naloxone (10(-10) and 10(8) M) in a competitive manner. The facilitation could also be counteracted by the addition of the kappa-receptor antagonist M(r) 2266 (10(-7) M). **Muscarinic** blockade, achieved with atropine (10(-6) M), did not alter the effect of dynorphin A (1-13). Addition of phentolamine mesylate (10(6) M), and propranolol (10(-6) M) per se facilitated the EFS-induced contractions. Both adrenergic blockade as well as the addition of the substance P blocker spantide, counteracted the facilitating effect of dynorphin A (1-13). In conclusion: Dynorphin A immunoreactive material was found to be present in nerves in the rat detrusor and in prevesical ganglia. Dynorphin A (1 13) facilitated the detrusor contraction, possibly via actions on kappa-opioid receptors and interaction with non-cholinergic nerves.

L12 ANSWER 54 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93063387 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1436123
TITLE: Quest for agonist and antagonist selectivity at **muscarinic** receptors in guinea-pig smooth muscles and cardiac atria.
AUTHOR: Dorofeeva N A; Shelkovnikov S A; Starshinova L A; Danilov A F; Nedoma J; Tucek S
CORPORATE SOURCE: Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg.
SOURCE: Naunyn Schmiedeberg's archives of pharmacology, (1992 Oct) 346 (4) 383-90. Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921201

AB Potencies of 11 **muscarinic** agonists in eliciting contraction of smooth muscle in guinea-pig ileum, trachea, **urinary bladder** and uterus and in **inhibiting** the rate of contractions of cardiac atria were compared. While acetylcholine (ACh) was the most potent agonist on the ileum, uterus and cardiac atria, cis-L(+)-dioxolane was equally as potent as ACh on the ileum and more potent on the **urinary bladder** and trachea. Compared to ACh, methylfurmethide, oxotremorine, acetoxybut-2-inyl-trimethylammonium and cis-L(+) dioxolane acted weakly on the atria. Arecclidine, arecoline and acetyl-beta-methylcholine displayed selectivity for the **urinary bladder** and pilocarpine for the tracheal and **urinary bladder** smooth muscles. Oxotremorine had very low activity on the uterus. The stereoselectivity of **muscarinic** ACh receptors (mAChRs) for cis-L(+)-and cis-D( ) dioxolane was low in the **urinary bladder** and uterus and high in the ileum and trachea. Most antagonists showed little selectivity between different organs, but S(-)-phenylcyclohexylglycoloyl choline was 6 times more active on the **urinary bladder** than on the ileum and AF-DX 116 was 12-30 times more active on the atria than on the smooth muscles. Among the N alkyl derivatives of benzilylcholine, the octyl derivative as 400 times more active on the ileum than on the atria, while among the N alkyl derivatives of QNB, the N-decyl derivative was 41 times more active on the ileum. The observed differences in the potency of various agonists and their stereoisomers on different smooth muscles cannot be explained by differences in the accessibility of receptors or in receptor reserve. (ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 55 OF 121 MEDLINE on STN
ACCESSION NUMBER: 93059868 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1433649
TITLE: Effect of tetrodotoxin on the phasic and tonic responses of isolated rabbit **urinary bladder** smooth muscle to field stimulation.
AUTHOR: Tammela T L; Wein A J; Levin R M
CORPORATE SOURCE: Division of Urology, University of Pennsylvania School of Medicine, Philadelphia.
CONTRACT NUMBER: P50-DK 39257 (NIDDK)
RO-1-DK 26508 (NIDDK)
RO-1-DK 33559 (NIDDK)
SOURCE: Journal of urology, (1992 Dec) 148 (6) 1937-40. Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921223

AB The response of the rabbit **urinary bladder** to field stimulation (80 volts, 2-32 Hz, 1 msec duration) is biphasic, consisting of an initial phasic contraction mediated by cholinergic and purinergic neurotransmitters, followed by a prolonged tonic contraction which is solely cholinergic. Obstructive hypertrophy of the **bladder** induces a variety of contractile alterations including a significantly greater reduction in the tonic component of the contractile response as compared to the phasic component. This results in a severe dysfunction in the ability of the **bladder** to empty. One possibility is that the inability of the **bladder** to maintain tension and empty efficiently may be related to a degeneration of nerves innervating the **bladder** smooth muscle. In addition to the well documented neuropathy, the **bladder** undergoes hypertrophy +/- hyperplasia of both smooth muscle and interstitial cellular elements, alterations in the metabolism of substrates, alterations in the synthesis of structural and smooth muscle proteins, and alterations in the deposition of collagen. The purpose of this study was to 1) to create a specific neuropathy in the absence of the additional structural, smooth muscle, and metabolic changes that are induced by partial outlet obstruction; and 2) determine if the contractile dysfunctions induced by the neuropathy have properties similar to the contractile dysfunctions induced by outlet obstruction. In the present study, a progressive "smooth muscle neuropathy" was induced in isolated strips of male rabbit **urinary bladder** smooth muscle by incubating isolated strips of **urinary bladder** body in the presence of increasing concentrations of tetrodotoxin (15-1500 nM). In these studies, we determined the effect of increasing concentrations of tetrodotoxin (TTX) on the response to field stimulation utilizing 2 Hz and 32 Hz, at 80 V and 1 ms duration. The effects of TTX on maximum rate of contraction, peak contraction and tonic contraction were monitored. In addition, the effects of atropine (cholinergic **muscarinic** blockage) and ATP-desensitization (purinergic **inhibition**) on the effects of TTX were also determined. The results can be summarized as follows: 1) Both atropine and ATP desensitization individually **inhibited** significantly the peak response to field stimulation. 2) Atropine abolished the tonic response. 3) TTX **inhibited** the tonic contraction at significantly lower concentrations than it **inhibited** peak contraction. Thus, at low concentrations of TTX, a condition similar to that seen in obstructive hypertrophy was created. 4) The ED50 in the presence of atropine was

L12 ANSWER 55 OF 121 MEDLINE on STN (Continued)
significantly greater than the ED50 following ATP desensitization. This may indicate that there are separate synaptic elements for cholinergic and purinergic transmission.(ABSTRACT TRUNCATED AT 400 WORDS)

L12 ANSWER 56 OF 121 MEDLINE on STN
ACCESSION NUMBER: 92395838 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1381764
TITLE: Selectivity of class I antiarrhythmic agents, disopyramide, pirmenol, and pentisomide for peripheral **muscarinic** M2 and M3 receptors.
AUTHOR: Endou M; Hattori Y; Gando S; Kanno M
CORPORATE SOURCE: Department of Pharmacology, Hokkaido University School of Medicine, Sapporo, Japan.
SOURCE: Journal of cardiovascular pharmacology, (1992 May) 19 (5) 674-81.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19921023
Last Updated on STN: 19980206
Entered Medline: 19921013

AB The interactions of the class I antiarrhythmic agents, disopyramide, pirmenol, and pentisomide with peripheral **muscarinic** receptors were investigated by binding assay with [3H]N-methylscopolamine ([3H]NMS) as a ligand. All the agents **inhibited** the specific [3H]NMS binding to membrane preparations obtained from guinea pig submandibular gland (SG) and **urinary bladder** (UB) smooth muscle. The competition curves of these agents for [3H]NMS binding to SG membranes were monophasic, indicating competition with [3H]NMS at a single site. Comparison of results with those of our previous binding experiments using guinea pig left atrial (LA) membranes, showed that pirmenol had sevenfold lower affinity for glandular-type **muscarinic** receptors (M3) than for cardiac-type **muscarinic** receptors (M2). On the other hand, the dissociation constants (Ki) for disopyramide and pentisomide in SG were comparable to the high-affinity Ki values for these agents at M2 receptors. The competition curves of the three agents for [3H]NMS binding to UB membranes were biphasic and showed high- and low-affinity states of binding. The high- and low-affinity Ki values for pirmenol in UB were similar to its Ki values at M2 and M3 receptors obtained in LA and SG, respectively. The high affinity Ki values for disopyramide and pentisomide were consistent with the respective Ki values determined in SG, whereas the low-affinity binding sites for these agents were presumably the result of their allosteric interactions with the receptors. All agents at higher concentrations slowed the dissociation of [3H]NMS elicited by an excess of atropine in both UB and SG, thus indicating allosteric interactions.(ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 57 OF 121 MEDLINE on STN
ACCESSION NUMBER: 92303044 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1819171
TITLE: [Acetylcholinesterase and the ADH-dependent transport of water in the amphibian **bladder**]. Atsetilkholinesteraza i ADG zavisimyi transport vody v mochevom puzyre amfibii.
AUTHOR: Bagrov Ia Iu; Manusova N B; Ostretsova I B
SOURCE: Tsitologiia, (1991) 33 (11) 141-52.
Journal code: 0417363. ISSN: 0041-3771.
PUB. COUNTRY: USSR
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920731
Last Updated on STN: 19920731
Entered Medline: 19920723

AB It was found that acetylcholine (ACh) at the concentration of 10(-3) M **inhibited** ADH-stimulated water transport through the wall of amphibian **urinary bladder**. This effect was suggested to be caused by an interaction of ACh with acetylcholinesterase (AChE) rather than by a stimulation of the M- or N-cholinoreceptor. The **inhibitory** action of ACh was completely suppressed in the presence of various AChE **inhibitors** (physostigmine, proserine, armine, Gd-42, acridine iodmethylate), while an **inhibitor** of butyrylcholinesterase (BuChE), AD-4, failed to affect it. In accord with this observation the activity of AChE (but not of BuChE) was demonstrated in the **urinary bladder** epithelium. Since, in addition to the hydrosmotic effects of pituitrine, 8-arginine-vasopressin or oxytocin, ACh blocked also effects of forskolin or cyclic AMP, one may conclude that it acts at some post-cyclic AMP production stage. AChE-dependent **inhibition** of the ADH-stimulated water transport decreased significantly when the serosal pH was raising from 7.2 to 8.0, but was augmented by serosal acidification (pH 6.8), whereas such pH alterations did not affect the activity of the epithelium AChE. The effect of ACh under consideration was suppressed by adding amiloride (10(-4) M) to the serosal solution. Similarly, the ACh effect was blocked by an **inhibitor** of Ca-dependent K+ channels, 4-aminopyrdine, which in addition prevented the **inhibition** of the ADH-stimulated water transport by the serosal acidification. It was noteworthy that some other K+ channel blockers (Ba2+, Cs+, tetraethylammonium, apamine, quinine) did not affect either the water transport or the antipituitrine effect of ACh. In conclusion, we suggest that the **inhibitory** action of ACh on the ADH-stimulated water transport in the **urinary bladder** is mediated through the intracellular acidification resulting from ACh interaction with AChE. It is unlikely that the acidification is merely a consequence of the ACh hydrolysis, rather the ACh-AChE interaction induces directly an increase in the proton conductivity of the basolateral membrane of the **urinary bladder** epithelium.

L12 ANSWER 58 OF 121 MEDLINE on STN
ACCESSION NUMBER: 92299927 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1607601
TITLE: Evidence for **inhibitory** nicotinic and facilitatory **muscarinic** receptors in cholinergic nerve terminals of the rat **urinary bladder**.
AUTHOR: Somogyi G T; de Groat W C
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh, Pennsylvania 15261.
CONTRACT NUMBER: DK 37241 (NIDDK)
DK 42369 (NIDDK)
MH 30915 (NIMH)
SOURCE: Journal of the autonomic nervous system, (1992 Feb) 37 (2) 89-97.
Journal code: 8003419. ISSN: 0165-1838.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920731
Last Updated on STN: 19920731
Entered Medline: 19920722

AB Cholinergic prejunctional modulatory receptors on parasympathetic nerves in the rat **urinary bladder** were studied by measuring 3H-acetylcholine (ACh) release in muscle strips from the **bladder** body. Electrical field stimulation markedly increased 3H-ACh overflow in strips preloaded with 3H-choline. Oxotremorine (1 microM), an M2 receptor agonist and DMPP (10 microM) a nicotinic (N) receptor agonist decreased the release of ACh (50% and 55% respectively); whereas McN-A 343 (50 microM) an M1 receptor agonist increased the release (33%), indicating the presence of three types of modulatory receptors. The anticholinesterase agent, physostigmine in concentrations of 1, 5 and 25 microM and neostigmine (5 microM) increased ACh release (44-710%). However a low concentration of physostigmine (0.05 microM) decreased release. Pirenzepine, an M1 **muscarinic** antagonist or atropine blocked the increased ACh release in physostigmine-treated strips, but in normal strips pirenzepine did not change release and atropine increased release. McN-A 343 or prolonged application (15 min) of DMPP increased ACh release (376% and 391% respectively) in physostigmine-treated strips. The response to McN-A 343 was blocked by pirenzepine. d-Tubocurarine (DTC), a nicotinic receptor blocker, enhanced ACh release in the presence of physostigmine but proved to be ineffective in normal preparations. These findings suggest that all three cholinergic receptors (M1 facilitatory, N **inhibitory** and M2 **inhibitory**) are activated by endogenous ACh in physostigmine treated preparations whereas only M2-**inhibitory** receptors are activated in normal preparations. It will be important in future studies to determine whether M1 and M2 mechanisms can also be activated under more physiological conditions in the **bladder** and whether they are present at other cholinergic synapses.

L12 ANSWER 59 OF 121 MEDLINE on STN
ACCESSION NUMBER: 92183654 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1724648
TITLE: (+/-)-Terodiline: an M1-selective **muscarinic** receptor antagonist. In vivo effects at **muscarinic** receptors mediating **urinary bladder** contraction, mydriasis and salivary secretion.
AUTHOR: Noronha-Blob L; Prosser J C; Sturm B L; Lowe V C; Enna S J
CORPORATE SOURCE: NOVA Pharmaceutical Corporation, Baltimore, MD 21224.
SOURCE: European journal of pharmacology, (1991 Aug 29) 201 (2-3) 135-42.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 19960129
Entered Medline: 19920416

AB The affinity and selectivity of racemic terodiline (N tert-butyl-1-methyl-3,3-diphenylpropylamine HCl) for **muscarinic** receptor subtypes was determined from functional responses of rabbit vas deferens (M1), guinea pig atria (M2) and **bladder** detrusor muscle (M3). (+/-)-Terodiline was found to be about as potent as pirenzepine in the rabbit vas deferens (Kb = 15 and 31 nM, respectively) and at least as selective for M1 relative to M2 (11-fold) and M3 (19-fold) receptors. Like pirenzepine, (+/-)-terodiline does not distinguish between M2 and M3 receptors in vitro. The peripheral actions of (+/) terodiline were evaluated in vivo in terms of its ability to induce mydriasis, and to **inhibit** salivary secretion and **urinary bladder** contraction. (+/-)-Terodiline given s.c. was equipotent in **inhibiting** intravesical **bladder** pressure and carbachol-induced salivary secretion (ID50 = 24 and 35 mg/kg, respectively), and in increasing pupil diameter (ED50 = 59 mg/kg). These results suggest that the in vivo actions of racemic terodiline at (M3) receptors mediating **bladder** contraction may not be separable from its actions at receptors mediating mydriasis and salivation. Moreover, its effects on the pupil and salivary glands are apparently not mediated through M1 receptors. Together, these findings help clarify the action of (+/-)-terodiline in the treatment of neurogenic **bladder** .

L12 ANSWER 60 OF 121 MEDLINE on STN
ACCESSION NUMBER: 92131842 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1775512
TITLE: Effects of pregnancy on **muscarinic** receptor density and function in the rabbit **urinary bladder**.
AUTHOR: Levin R M; Zderic S A; Ewalt D H; Duckett J W; Wein A J
CORPORATE SOURCE: Division of Urology, Hospital of the University of Pennsylvania, Philadelphia.
CONTRACT NUMBER: RO-1 DK26508 (NIDDK)
RO-1 DK33559 (NIDDK)
RO1 DK39086 (NIDDK)
+
SOURCE: Pharmacology, (1991) 43 (2) 69-77.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920322
Last Updated on STN: 19970203
Entered Medline: 19920305

AB The contractile response of the rabbit **urinary bladder** to field stimulation consists of both cholinergic and purinergic components. In general, approximately 60% of the contractile response to field stimulation is cholinergic and 40% is purinergic. Although the purinergic response represents a significant proportion of the initial (phasic) pressure response to field stimulation of the isolated whole **bladder**, it contributes only 10 15% of the ability of field stimulation to empty the **bladder**. The current study investigates the effects of pregnancy on the contractile responses of the isolated **urinary bladder** to cholinergic and purinergic stimulation. The results of these studies indicate that pregnancy induces substantial changes in the physiology and pharmacology of the **urinary bladder**. The following data are consistent with the theory that pregnancy substantially increases the relative purinergic component of the response to field stimulation (and presumably neuronal stimulation): (1) there was a significantly greater response of the **bladders** isolated from pregnant rabbits to low-frequency field stimulation; (2) atropine was more effective at **inhibiting** the pressure generation of **bladders** isolated from virgin female rabbits; (3) field stimulation was more effective at emptying **bladders** isolated from virgin female rabbits; (4) the response of the **bladders** from pregnant rabbits to bethanechol was significantly reduced, whereas the response to ATP was significantly increased. In addition to these effects of pregnancy on **bladder** physiology, pregnancy induced a 50% decrease in the **muscarinic** receptor density of the **urinary bladder** body, which correlated very well with the 50% decrease in the contractile response to bethanechol.

L12 ANSWER 61 OF 121 MEDLINE on STN
ACCESSION NUMBER: 92070820 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1959843
TITLE: Pharmacological analysis of drug interactions of disopyramide and its congeners with peripheral **muscarinic** acetylcholine receptors.
AUTHOR: Endou M
CORPORATE SOURCE: Department of Pharmacology, Hokkaido University School of Medicine, Sapporo, Japan.
SOURCE: [Hokkaido igaku zasshi] Hokkaido journal of medical science, (1991 Sep) 66 (5) 677-93.
Journal code: 17410290R. ISSN: 0367-6102.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199201
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19980206
Entered Medline: 19920109

AB The interactions of the antiarrhythmic agents, disopyramide (D) and its congeners, pirmenol (Pr) and pentisomide (Pt), with peripheral **muscarinic** receptors (m-AchR) were investigated using binding and functional assays. D, Pr and Pt **inhibited** the specific binding of [3H]-N-methyl scopolamine ([3H]-NMS) to membrane fractions prepared from guinea pig left atria (LA), submandibular glands (SG) and **urinary bladders** (UB) in a concentration-dependent manner. Computer-assisted analysis showed that the displacement curves with D obtained from LA and UB were shallow and best fitted by a two-site model, whereas D interacted with a single class of binding sites in SG. Kinetic experiments measuring [3H]-NMS dissociation revealed the existence of allosteric interaction of D with m-AChR, and it might be responsible for the low affinity components of the displacement curves in LA and UB. The pKi values for D in high-affinity receptor sites in LA and UB (pKH) were very close to the pKi for D obtained in SG, and corresponded well to the pA2 values of around 6.0 for antagonism against the carbachol-induced mechanical responses of LA and UB. Pt interacted with m-AChR with qualitatively very similar fashion to that of D, but its potency was very weak (1/10 of D). Pr interacted with a single class of binding sites in LA and SG with pKi of 6.02 and 5.18, respectively, indicating that the affinity of Pr to glandular m-AChR (M3) was 7 fold lower than that to cardiac one (M2). The displacement curve with Pr in UB was best fitted by a two-site model with pKH of 5.93 and pKL of 5.20. The pA2 for Pr in LA and UB were 6.47 and 5.55, respectively, suggesting the existence of a mixed population of M2 and M3 in UB and the contribution of M3 to its contractile response. It is concluded that Pr is able to distinguish M2 from M3, and that D and Pt have almost similar affinity to both subtypes of m-AChR. Pr was less potent than D in interaction with M3.

L12 ANSWER 62 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91339907 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1651865
TITLE: Effect of extracellular Ca2+ on cholinergic, KCl and phorbol ester-mediated phosphoinositide turnover and guinea pig **urinary bladder** contraction.
AUTHOR: Lowe V C; Noronha-Blob L
CORPORATE SOURCE: Nova Pharmaceutical Corporation, Baltimore, MD 21224.
SOURCE: European journal of pharmacology, (1991 Mar 26) 195 (2) 273-9.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911013
Last Updated on STN: 19911013
Entered Medline: 19910920

AB The effect of extracellular Ca2+ ([Ca2+]o) on cholinergic, KCl and phorbol ester-mediated detrusor contractions was related to phosphoinositide (PI) breakdown in guinea pig **urinary bladder**. Carbachol (1.0 mM) elicited a 20 fold increase in inositol phosphate (IP) accumulation both in presence and absence of [Ca2+]o yielding the same EC50 value (approximately 12 microM). In contrast, carbachol-induced detrusor contractions were reduced by 35% without [Ca2+]o, but maximal efficacy was restored with Ca2+ replenishment. In absence of [Ca2+]o, repeated cholinergic stimulation yielded contractions only if tissues were intermittently equilibrated in [Ca2+]o. High K+ and PDBu evoked [Ca2+]o-dependent contractions. Ca2+ channel antagonists and divalent metal cations **inhibited** high K+ more potently than carbachol-mediated contractions. Together, these findings suggest multiple sources of Ca2+ for **urinary bladder** contraction, where voltage-sensitive responses depend primarily on [Ca2+]o and PI-linked **muscarinic** responses involved Ca2+ mobilization from intracellular stores as well. Clinical agents used for the treatment of **urinary** incontinence **inhibited** both carbachol-induced PI turnover and muscle contraction with the same rank order of potency both in presence and absence of [Ca2+]o. These findings suggest that the cholinergic mechanism of action of these agents involves the PI-Ca2+ effector system.

L12 ANSWER 63 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91279839 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2057522
TITLE: Comparison of the contractile and metabolic effects of **muscarinic** stimulation with those of KCl.
AUTHOR: Levin R M; Hypolite J; Longhurst P A; Wein A J
CORPORATE SOURCE: Division of Urology, University of Pennsylvania School of Medicine, Philadelphia.
CONTRACT NUMBER: P-50-DK 39257 (NIDDK)
RO-1-DK 26508 (NIDDK)
RO-1-DK 33559 (NIDDK)
SOURCE: Pharmacology, (1991) 42 (3) 142-50.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910818
Last Updated on STN: 19910818
Entered Medline: 19910801

AB **Urinary bladder** emptying is mediated primarily by a coordinated contraction of the **bladder** body in response to parasympathetic stimulation and **muscarinic** receptor activation. In previous studies we presented evidence that the contractile response to bethanechol stimulation could be dissociated from the metabolic response through the use of diltiazem (calcium channel blockade). The conclusion from these studies was that **muscarinic** stimulation resulted in a significant increase in metabolic activity which was not directly associated with contraction. KCl stimulates contraction in isolated strips by directly depolarizing the membrane rather than from binding to specific membrane receptors. The current study directly compares the metabolic and contractile activity of bethanechol (**muscarinic** stimulation) with KCl (direct membrane depolarization). Isolated strips of rabbit **urinary bladder** body were monitored in vitro for changes in intracellular-free calcium, NADH/NAD ratio, and contraction. Intracellular-free calcium was monitored by preincubation of isolated **bladder** smooth muscle strips with FURA-2 AM and continuously measuring the fluorescence with an MB2 surface spectrofluorometer using excitation wavelengths of 340 and 380 nm, and an emission wavelength of 510 nm. The NADH/NAD ratio was monitored with the MB2 surface spectrophotometer using an excitation wavelength of 366 nm and an emission wavelength of 450 nm. Contraction was monitored using a isometric force transducer connected to a Grass model D polygraph. The results can be summarized as follows. (1) Both bethanechol and KCl stimulate a sharp decrease in the NADH/NAD ratio, a rapid increase in intracellular-free calcium, and a slower increase in contractile force. (ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 64 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91259787 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1828510
TITLE: Biochemical and functional characteristics of **bladder muscarinic** receptors and effects of experimental diabetes in rats.
AUTHOR: Morita T
CORPORATE SOURCE: Department of Urology, Akita University School of Medicine.
SOURCE: Nippon Hinyokika Gakkai zasshi. japanese journal of urology, (1991 Jan) 82 (1) 52-60.
Journal code: 2984841R. ISSN: 0021-5287.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910802
Last Updated on STN: 19910802
Entered Medline: 19910716

AB **Bladder** dysfunction is a common complication of diabetes mellitus and is attributed in part to peripheral neuropathy. Voiding function is mainly controlled by **muscarinic** receptor function. Therefore, I investigated first the biochemical and functional characteristics of **urinary bladder muscarinic** receptors and then the effects of experimental diabetes on them. Experimental diabetes was induced in 2 month-old male rats by intravenous injection of 65 mg/kg of streptozotocin (STZ). Effects of diabetes mellitus were investigated 2, 4 and 8 weeks after injection of STZ. The amount of **muscarinic** receptors labelled with 3H-quinuclidinyl benzylate (QNB) was higher in the **bladder** dome of diabetic animals than control animals, while the affinity for its binding sites was similar in both groups. **Muscarinic** agonists and antagonists **inhibited** 3H-QNB binding with similar **inhibitory** constants (Ki) in control and diabetic domes. The rank order of **inhibition** of 3H-QNB binding by **muscarinic** agonists and antagonists: bethanechol greater than pirenzepine greater than carbamylcholine greater than acetylcholine greater than atropine, is consistent with the absence of M1 receptors in the **bladder** dome. In functional studies **muscarinic** agonists induced a larger contractile response in **bladder** dome muscle strips from 8 week-old diabetic animal than those from controls. The rank order of ED50s were similar in the control and treated groups, being in good agreement with the Ki values obtained from receptor binding studies. These data show a direct correlation between the diabetes-induced biochemical and functional alterations in **muscarinic** receptor properties of the rat **bladder.**

L12 ANSWER 65 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91192889 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1672862
TITLE: DuP 753 is a specific antagonist for the angiotensin receptor.
AUTHOR: Rhaleb N E; Rouissi N; Nantel F; D'Orleans-Juste P; Regoli D
CORPORATE SOURCE: Department of Pharmacology, Medical School University of Sherbrooke, Quebec, Canada.
SOURCE: Hypertension, (1991 Apr) 17 (4) 480-4.
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 19910602
Last Updated on STN: 19980206
Entered Medline: 19910513

AB 2-n-Butyl-4-chloro-5-hydroxy-methyl-1-[(2'-(1H)-tetrazol-5-yl)biph enyl-4-yl)methyl]imidazol potassium salt (DuP 753) is a nonpeptide angiotensin II receptor antagonist that **inhibits** the contractile effects of angiotensin II competitively and shows pA2 values of 8.27 on the rabbit aorta and jugular vein, 8.66 on the rat portal vein and stomach, 8.19 on the rat **urinary bladder**, and 8.36 on human colon, ileum, and **urinary bladder**. This agent (more than 10(-5) M) exhibits no agonistic activity and does not affect the contractile effects of norepinephrine, acetylcholine, bradykinin, desArg9-bradykinin, substance P, neurokinin A, neurokinin B, or bombesin in the various tissues. The present results demonstrate that DuP 753 is a potent nonpeptide antagonist with high affinity, specificity, and selectivity for the angiotensin receptor.

L12 ANSWER 66 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91132462 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1993995
TITLE: Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2 and M3 **muscarinic** receptors and in vivo effects on **urinary bladder** contraction, mydriasis and salivary secretion in guinea pigs.
AUTHOR: Noronha-Blob L; Kachur J F
CORPORATE SOURCE: Nova Pharmaceutical Corporation, Baltimore, Maryland.
SOURCE: Journal of pharmacology and experimental therapeutics, (1991 Feb) 256 (2) 562-7.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910405
Last Updated on STN: 19970203
Entered Medline: 19910321

AB The major side effects of racemic oxybutynin (OXY), which is used in the treatment of **urinary** incontinence are dry mouth (xerostomia) and blurred vision (mydriasis). Highly purified enantiomers of OXY [(R)OXY, (S)OXY] were compared with the racemate both in vitro in functional studies and in vivo in guinea pigs to evaluate their pharmacological action relative to their adverse effects. The affinity of (R)OXY and (S)OXY for different **muscarinic** receptor subtypes was determined using field stimulated rabbit vas deferens (M1) and guinea pig atria (M2) or **bladder** (M3) strips. Stereoselective antimuscarinic effects [(R)OXY greater than or equal to (R/S) OXY much greater than (S)OXY] were evident at all three receptor subtypes; the isomeric ratio [(S)OXY/(R)OXY] ranged from 12 to 88. Both (R)OXY and (R/S)OXY were slightly more selective (2 4 fold, P less than .01) for M1 and M3 relative to M2 **muscarinic** receptors. Stereoselectivity was also evident in vivo for volume-induced **urinary bladder** contractions as measured by cystometrogram parameters [(S)OXY/(R)OXY approximately 21], mydriasis [(S)OXY/(R)OXY approximately 136] and salivary gland secretory responses [(S)OXY/(R)OXY approximately 30]. The absolute potencies of (R)OXY or (R/S)OXY for mydriasis and salivation were similar to those for **inhibition** of intravesical **bladder** pressure. Also, (R)OXY and (R/S)OXY equipotently antagonized cholinergic-mediated CNS effects in mice. Collectively, the data suggest that the activity of (R/S)OXY resides predominantly in the (R)-enantiomer. However, it appears that (R)OXY may offer no significant pharmacological advantage over (R/S)OXY in terms of its principal therapeutic and side effect profile.

L12 ANSWER 67 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91081462 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2175437
TITLE: **Muscarinic** cholinergic antibody in experimental autoimmune myocarditis regulates cardiac function.
AUTHOR: Paaerez Leiros C; Sterin-Borda L; Cossio P; Borda E S
CORPORATE SOURCE: Centro de Estudios Farmacologicos y Botanicos (CEFYBO) (ex-CEFAPRIN), CONICET, Buenos Aires, Argentina.
SOURCE: Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N. Y.), (1990 Dec) 195 (3) 356-63. Journal code: 7505892. ISSN: 0037-9727.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910322
Last Updated on STN: 19910322
Entered Medline: 19910129

AB Evidence is presented showing that in experimental autoimmune myocarditis, there are certain components in IgG fraction of the sera that bind to myocardium **muscarinic** cholinergic receptors. The autoimmune IgG simulated the biologic effect of cholinergic agonists because (i) it increased cGMP levels, (ii) it decreased cAMP stimulated levels, and (iii) it reduced heart contractility and diminished reactivity to exogenous acetylcholine. Autoimmune IgG **inhibited** the binding of specific **muscarinic** cholinergic radioligand to purified myocardial membranes behaving as noncompetitive **inhibitors**. The recognition appears to be organ specific because the autoimmune IgG did not bind to **muscarinic** cholinergic receptors of **urinary bladder**. The presence of antibodies against antigens expressed in an accessible form to antibody in living myocardial cells might be related to some of the immunopathologic mechanisms participating in the pathogenesis of the experimental autoimmune myocarditis.

L12 ANSWER 68 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91077650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2257437
TITLE: High- and low-affinity binding sites for [3H]-alpha, beta-methylene ATP in rat **urinary bladder** membranes.
AUTHOR: Bo X N; Burnstock G
CORPORATE SOURCE: Department of Anatomy and Developmental Biology, University College London.
SOURCE: British journal of pharmacology, (1990 Oct) 101 (2) 291-6. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910322
Last Updated on STN: 19970203
Entered Medline: 19910131

AB 1. The characteristics of [3H]-alpha, beta-methylene adenosine 5'triphosphate ([3H]-alpha, beta MeATP) binding to membrane preparations of rat **urinary bladder** detrusor were studied. 2. The rat **bladder** membrane preparation was obtained by multiple centrifugation. [3H]-quinuclidinyl benzilate ([3H]-QNB) binding to this preparation demonstrated that the **muscarinic** receptor density was 4.32 times higher than that in the homogenate. [3H] alpha, beta-MeATP binding was increased 3.88 times. 3. Saturation analysis revealed that the rat **bladder** membrane contained a high density of [3H]-alpha, beta MeATP binding sites, which could be divided into a high affinity component (Kd = 8.1-8.9 nM) and a low-affinity component (Kd = 67.0-119.8 nM). 4. Magnesium ions **inhibited** the maximum binding in a concentration-dependent manner. The maximum high-affinity binding was reduced from 10.32 pmol mg-1 protein in magnesium-free buffer to 4.62 pmol mg-1 protein with 25 mM MgCl2, while the maximum low-affinity binding was reduced from 58.84 pmol mg-1 protein to 14.24 pmol mg-1 protein. Kd values were not greatly affected. 5. The binding was a rapid reversible process. The association rate constants were 7.64 x 10(7) M-1 min-1 for high-affinity binding, and 7.31 x 10(6) M-1 min-1 for low-affinity binding. The dissociation rate constants were 0.2896 min-1 for high-affinity binding, and 0.6348 min-1 for the low-affinity binding. 6. Displacement experiments with unlabelled purinoceptor ligands confirmed that [3H]-alpha, beta-MeATP mainly binds to P2X-purinoceptors. (ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 69 OF 121 MEDLINE on STN
ACCESSION NUMBER: 91067580 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2351221
TITLE: Characterization of **muscarinic** cholinergic receptors in membrane preparations from rat prostatic adenocarcinoma.
AUTHOR: Batra S; Christensson P I; Hartley-Asp B
CORPORATE SOURCE: Department of Cancer Pharmacology, Pharmacia LEO Therapeutics AB, Helsingborg, Sweden.
SOURCE: Prostate, (1990) 17 (4) 261-8. Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910308
Last Updated on STN: 19970203
Entered Medline: 19910117

AB The binding characteristics of 3H quinuclidinyl benzilate (QNB) to **muscarinic** sites in isolated plasma membrane fractions from R-3327 Dunning tumors (H and AT-1 sublines), ventral, dorsolateral prostate; and **urinary bladder** of the rat were studied. QNB binding to all preparations, except from AT-1 tumors, was specific, saturable, and of high affinity. The AT-1 tumors completely lacked specific QNB binding. The **muscarinic** receptor density in H tumors was twofold and twentyfold higher than that in the ventral prostate and dorsolateral prostate respectively. The receptor density in the **urinary bladder** was approximately twofold higher than that in H tumors. The Kd values in H tumors and ventral prostate were very similar and significantly higher than that in dorsolateral prostate or the **urinary bladder**. QNB binding in H tumors was strongly **inhibited** by classical **muscarinic** receptor antagonists atropine and scopolamine, but poorly by the agonists carbacholine and pilocarpine. In contrast to scopolamine or atropine, **inhibition** by pirenzepine and AF-DX116 was relatively low. These data indicate that the **muscarinic** receptor in Dunning H tumors is of M3 type.

L12 ANSWER 70 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90384910 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2402477
TITLE: Effects of some antidepressants on the volume-induced reflex contractions of the rat **urinary bladder**: lack of correlation with **muscarinic** receptors affinity.
AUTHOR: Pietra C; Poggesi E; Angelico P; Guarneri L; Testa R
CORPORATE SOURCE: Pharmacology Department, RECORDATI S.p.A., Milan, Italy.
SOURCE: Pharmacological research : official journal of the Italian Pharmacological Society, (1990 Jul-Aug) 22 (4) 421-32. Journal code: 8907422. ISSN: 1043-6618.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901122
Last Updated on STN: 19970203
Entered Medline: 19901023

AB It has been suggested that tricyclic antidepressants such as imipramine, might exert their anti-enuretic action by a blockade of **muscarinic** receptors in the detrusor muscle of the **urinary bladder**. We have therefore investigated the effects of two tricyclic (imipramine and nortriptyline) and three atypical (citalopram, amineptine and mianserin) antidepressants on the micturition reflex and **muscarinic** receptors in rats. The micturition reflex pathway was monitored indirectly by recording the rhythmic intravesical pressure waves which occurred when the **bladder** was distended and maintained under constant saline-volume. The activity of the antidepressants was correlated to their potencies as antagonists of [3H]QNB binding to rat brain (mainly M1 receptors) and **bladder** (mainly M2 receptors) membranes, as well as antagonists of carbachol-induced contractions of rat **bladder** strips. Only imipramine and citalopram dose dependently **inhibited** the voiding contractions, whereas nortriptyline, imipramine and mianserin (in order of potency) were active both in binding studies and as competitive antagonists of carbachol-induced **bladder** contractions, but were inactive in **inhibiting** the micturition reflex. The present data seem to suggest that affinities for **muscarinic** receptors are unrelated to the **inhibition** of micturition reflex.

L12 ANSWER 71 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90315725 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2369797
TITLE: Interaction of antiestrogens with binding sites for **muscarinic** cholinergic drugs and calcium channel blockers in cell membranes.
AUTHOR: Batra S
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University Hospital, Lund, Sweden.
SOURCE: Cancer chemotherapy and pharmacology, (1990) 26 (4) 310-2. Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900921
Last Updated on STN: 19900921
Entered Medline: 19900822

AB The interaction of tamoxifen and clomifene with membrane binding sites for the cholinergic ligand quinuclidinyl benzilate (QNB) and the dihydropyridine calcium antagonist nitrendipine was studied. Both tamoxifen and clomifene competed with [3H]-QNB and [3H]-nitrendipine for their binding to the receptor in the membrane fractions from the **urinary bladder** and myometrium. The extent of **inhibition** as judged by the Ki values for both antiestrogens was similar at both receptor sites. The data suggest that the antiproliferative effects of tamoxifen may involve not only the intracellular estrogen-receptor system but also receptors for neurotransmitters and membrane calcium channels.

L12 ANSWER 72 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90277703 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2161851
TITLE: Atropine resistant transmission in partially depolarized rat **urinary bladder.**
AUTHOR: Carpenter F
CORPORATE SOURCE: Department of Pharmacology, University of Alabama, Birmingham 35294.
SOURCE: Journal of autonomic pharmacology, (1990 Apr) 10 (2) 97-107. Journal code: 8106455. ISSN: 0144-1795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 19900824
Last Updated on STN: 19900824
Entered Medline: 19900716

AB 1. Phasic contractile responses of the intact rat **urinary bladder** to the **muscarinic** agonists carbachol and pilocarpine became nearly blocked as the concentrations were progressively increased to 200-500 microM. In contrast, tonic contractile responses remained elevated throughout progressive increases in agonist concentration. 2. Nerve-induced phasic contractions to 1 Hz stimuli were potentiated throughout progressive increases in the concentration of **muscarinic** agonists. However, these responses were more atropine sensitive than untreated controls and responses to 1 Hz stimuli were nearly abolished. 3. After **inhibition** of **cholinesterase**, the action of cholinergic transmitter released during prolonged nerve stimulation may extend to the tonic contractile state of the **bladder** and potentiate responses to 1H stimuli. Nerve-induced responses were more atropine sensitive than untreated controls. 4. **Bladder** tone was increased and nerve-induced contractions to 1 Hz stimuli were also potentiated in an elevated K+ environment. However, atropine sensitivity of nerve-induced responses w s reduced. 5. Nerve-induced **bladder** contractions were linked to the tonic contractile state of the **bladder** muscle, controlled physiologically by **muscarinic** receptors. Since phasic contractile responses to **muscarinic** agonists were abolished at high concentrations by receptor desensitization, nerve-induced responses must be elicited under these conditions by a non-cholinergic transmitter.

L12 ANSWER 73 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90250642 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2338651
TITLE: Autonomic receptors in **urinary** tract: sex and age differences.
AUTHOR: Latifpour J; Kondo S; O'Hollaren B; Morita T; Weiss R M
CORPORATE SOURCE: Section of Urology, Yale University School of Medicine, New Haven, Connecticut.
CONTRACT NUMBER: DK 38311 (NIDDK)
SOURCE: Journal of pharmacology and experimental therapeutics, (1990 May) 253 (2) 661-7. Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199006
ENTRY DATE: Entered STN: 19900720
Last Updated on STN: 19900720
Entered Medline: 19900621

AB As age and sex affect the function of the lower **urinary** tract, we studied the characteristics of adrenergic and cholinergic receptors in various parts of lower **urinary** tract smooth muscle of young (6 months) and old (4 1/2-5 years) male and female rabbits. Saturation experiments performed with [3H]prazosin, [3H]yohimbine, [3H]dihydroalprenolol and [3H]quinuclidinyl benzylate in rabbit **bladdar** base, **bladder** dome and urethra indicate the presence of regional, sex- and age-related differences in the density of alpha-1, alpha-2, and beta adrenergic and **muscarinic** cholinergic receptors. Alpha 2 adrenergic receptor density is considerably higher in the female than in the male urethra of both age groups, whereas the higher density of beta adrenergic receptors in the female than in the male **bladder** base is observed only in the younger animals. The density of **muscarinic** receptors is higher in **bladder** dome than in **bladder** base or urethra in young rabbits of both sexes. In the old animals, the density of **muscarinic** receptors in **bladder** base increases to the level observed in **bladder** dome. **Inhibition** experiments with selective adrenergic agonists and antagonists indicate that the pharmacological profiles of alpha-2 adrenergic receptors in the urethra and beta adrenergic receptors in the **bladdar** dome and **bladder** base are similar in both sexes and at both ages. Beta-2 adrenergic receptors are shown to be predominant in **bladder** base and **bladdar** dome of rabbits. Parallel studies in rabbit urethra, adult rat cortex and neonatal rat lung show that the urethral alpha 2 adrenergic receptors are of the alpha-2A subtype.

L12 ANSWER 74 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90165615 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2483045
TITLE: Mechanism of action of nicotine in isolated **urinary bladder** of guinea-pig: involvement of tachykinin(s) released by nicotine in the drug's sympathomimetic effect.
AUTHOR: Hisayama T; Shinkai M; Takayanagi I; Toyoda T
CORPORATE SOURCE: Department of Chemical Pharmacology, Toho University School of Pharmaceutical Sciences, Chiba, Japan.
SOURCE: Archives internationales de pharmacodynamie et de therapie, (1989 Sep-Oct) 301 277-84. Journal code: 0405353. ISSN: 0301-4533.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19960129
Entered Medline: 19900319

AB A sympathetic neurone blocking drug, guanethidine, and a tachykinin antagonist, [D-Arg1, D-Pro2, D-Trp7,9, Leu11]-substance P (rpwwL-SP), partially **inhibited** the contractile response to nicotine to the same degree in the isolated detrusor strips of guinea pig **urinary bladder.** Application of rpwwL-SP completely abolished the **inhibitory** effect of guanethidine on the nicotine-induced contraction, suggesting that the tachykinin(s)-ergic transmission might be involved in the sympathomimetic effect of nicotine. Conversely, when the preparation was treated with guanethidine to block release of a mediator from the sympathetic nerve, the **inhibitory** effect of rpwwL-SP was diminished, suggesting an exclusive contribution of the sympathetic nerve communications to the action of the tachykinin(s). We previously suggested that nicotine may release acetylcholine and ATP to contract the detrusor strips, and that acetylcholine output may be increased by an unknown substance released from the sympathetic nerve by nicotine. In preparations treated with atropine, rpwwl-SP had no effect on the nicotine-induced contraction. The concentration-response curves for carbachol and ATP were not influenced by rpwwl-SP. After tachyphylaxis to capsaicin developed, the nicotine-induced contraction was not affected. It is suggested that in guinea-pig detrusor, tachykinin(s) from capsaicin-insensitive sites is (are) involved in the excitatory sympathomimetic effect of nicotine, and that the tachykinin(s) behave(s) as a modulator finally to increase the acetylcholine output from the parasympathetic cholinergic nerve.

L12 ANSWER 75 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90130540 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2613733
TITLE: Effects of selective cholinergic antagonists and alpha,beta-methylene ATP on guinea-pig **urinary bladder** contractions in vivo following pelvic nerve stimulation.
AUTHOR: Peterson J S; Noronha-Blob L
CORPORATE SOURCE: Nova Pharmaceutical Corporation, Baltimore, Maryland 21224-2788.
SOURCE: Journal of autonomic pharmacology, (1989 Oct) 9 (5) 303-13. Journal code: 8106455. ISSN: 0144-1795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900305

AB 1. An in vivo preparation measuring functional detrusor muscle strength in terms of intravesical **bladder** pressure (Pves) following in situ pelvic nerve stimulation has been developed in urethane-anaesthetized guinea pigs. 2. The increase in **bladder** pressure following pelvic nerve stimulation was abolished by topical lidocaine or tetrodotoxin, suggesting a neurogenic origin for the in vivo contractile response. 3. Cholinergic antagonists (i.v.) decreased the amplitude of the peak pressure response by about 50% at both high (30 Hz) and low (5 Hz) stimulation rates, with a rank order of potency of atropine greater than propantheline greater than oxybutynin greater than hexahydrosiladifenidol greater than pirenzepine greater than methoctramine. 4. The P2 purine receptor antagonist, alpha,beta-methylene ATP (i.v.), antagonized pelvic nerve stimulated **bladder** contractions differentially at 5 and 30 Hz. At low frequencies, alpha, beta-methylene ATP was both more potent (2.5-fold) and more efficacious (-77 compared to -55% delta) than at 30 Hz. Atropine and alpha,beta-methylene ATP together completely **inhibited** the contractile response. 5. Together, the findings indicate that in guinea pigs, **urinary bladder** contractions induced by pelvic nerve stimulation in vivo may be mediated by both **muscarinic** and purinergic receptors and that these **bladder** contractions may be mediated by the M2 beta subtype rather than by M1 or M2 alpha **muscarinic** receptors.

L12 ANSWER 76 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90095937 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2600844
TITLE: Enkephalinergic **inhibition** in parasympathetic ganglia of the **urinary bladder** of the cat.
AUTHOR: de Groat W C; Kawatani M
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, University of Pittsburgh, PA 15261.
CONTRACT NUMBER: AM 316888 (NIADDK)
MH 30915 (NIMH)
NS 25254 (NINDS)
SOURCE: Journal of physiology, (1989 Jun) 413 13-29. Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199001
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19900129

AB 1. Repetitive stimulation (10-20 Hz, 0.5-5 s duration) of the preganglionic nerves to ganglia on the surface of the **urinary bladder** of the cat produced a prolonged **inhibition** (duration, 30-65 s) of the postganglionic action potentials, elicited by low-frequency stimulation (0.25-1 Hz) of another preganglionic nerve to the same ganglion. 2. Intra-arterial administration of naloxone, an opiate antagonist (20-50 micrograms/kg), reduced the magnitude and duration of this heterosynaptic **inhibition** and also blocked the depression of ganglionic transmission elicited by the intra-arterial administration of leucine-enkephalin (0.1 10 micrograms/kg). 3. Naloxone did not alter adrenergic **inhibition** elicited by repetitive stimulation of the hypogastric nerve or exogenous noradrenaline. Naloxone did not alter the postganglionic firing elicited by single stimuli or trains of low-frequency (1 3 Hz) stimuli to the preganglionic nerves. 4. Heterosynaptic **inhibition** was not altered by the administration of antagonists for alpha-adrenergic (dihydroergotamine, prazosin, yohimbine), **muscarinic** (atropine), purinergic (theophylline) or GABAergic (picrotoxin) receptors. 5. A delta-selective opiate receptor agonist, DSLET (D-Ser2-leucine-enkephalin Thr), **inhibited** parasympathetic ganglionic transmission in low doses (mean threshold dose, 0.02 microgram/kg, I.A.), whereas a mu-opiate receptor agonist, morphine sulphate, produced only a small depression in larger doses (mean threshold dose, 100 micrograms/kg, I.A.). Ethylketocyclazocine, which has an affinity for kappa-receptors did not alter transmission in relatively large doses (1 mg/kg, I.A.). 6. These findings coupled with previous immunocytochemical demonstrations of leucine-enkephalin-like immunoreactivity in preganglionic nerve terminals in **bladder** ganglia suggest that opioid peptides released endogenously from preganglionic nerves are involved in delta receptor-mediated **inhibitory** mechanisms at cholinergic synapses in **bladder** ganglia.

L12 ANSWER 77 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90074839 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2480167
TITLE: Multiple sources of calcium for contraction of the human **urinary bladder** muscle.
AUTHOR: Maggi C A; Giuliani S; Patacchini R; Turini D; Barbanti G; Giachetti A; Meli A
CORPORATE SOURCE: Pharmacology Department, Res. Labs., A. Menarini Pharmaceuticals, Florence, Italy.
SOURCE: British journal of pharmacology, (1989 Nov) 98 (3) 1021-31. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199001
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19900125

AB 1. KCl, carbachol, neurokinin A and endothelin produced concentration-dependent contractions of mucosa-free muscle strips from the dome of the human **urinary bladder.** The maximal response to carbachol or neurokinin A exceeded that to KCl, while the maximal response to endothelin approached that to KCl. 2. Nifedipine (1 microM) abolished the response to KCl, reduced the response to carbachol or neurokinin A but had no effect on the response to endothelin. Bay K 8644 (1 microM) markedly potentiated the response to KCl but had little or no effect on the response produced by the other stimulants. 3. Superfusion of the strips with a nominally calcium (Ca)-free medium containing EDTA (1 mM) for 30 min markedly reduced the response to carbachol, neurokinin A and endothelin, although a small response was still evident at high concentrations. Likewise, after a prolonged (60 min) superfusion of the strips with a high K (80 mM) Ca-free medium plus EDTA (1 mM) these three agonists still produced a small contractile response. 4. The nifedipine (1 microM) resistant response to carbachol, neurokinin A or endothelin was markedly depressed by LaCl3 (1 mM). In contrast, the nifedipine-(1 microM) resistant response to carbachol was not modified by NiCl2 (0.1 mM) or omega-conotoxin (0.1 microM). 5. Caffeine produced divergent effects depending upon the temperature of incubation: a relaxation at 37 degrees C and a concentration-dependent (2.5-20 mM) contraction at 25 degrees C. The latter was markedly **inhibited** by procaine (3 mM) but unaffected by nifedipine (1 microM). 6. After a prolonged (60 min) superfusion with a high K, Ca-free medium containing EDTA the response to carbachol (100 microM) was abolished by previous exposure to procaine (3 mM). Conversely, the response to endothelin (1 microM) was unaffected by procaine. The response to endothelin in these experimental conditions was also resistant to LaCl3 (1 mM). 7. These findings indicate that multiple sources of Ca are mobilized for contraction of the human **bladder** muscle by different stimulants. Dihydropyridine- and voltage-sensitive Ca channels provide the major if not the sole source of Ca for the response to KCl, play some role in the response to **muscarinic** (carbachol) or NK-2 tachykinin receptor stimulation but are not involved in the response to endothelin. Carbachol, neurokinin A and endothelin all mobilize a Ca pool (either extracellular or located at membrane level) which is LaCl3-sensitive but nifedipine-resistant. Neither T- nor N type channels appear to be involved in the response to carbachol. (ABSTRACT TRUNCATED AT 400 WORDS)

L12 ANSWER 78 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90064117 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2573724
TITLE: Reorganization of sympathetic preganglionic connections in cat **bladder** ganglia following parasympathetic denervation.
AUTHOR: de Groat W C; Kawatani M
CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh, PA 15261.
CONTRACT NUMBER: AM 316888 (NIADDK)
MH 30915 (NIMH)
NS 25254 (NINDS)
SOURCE: Journal of physiology, (1989 Feb) 409 431-49. Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199001
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19900105

AB 1. Experiments were undertaken to examine the mechanisms involved in the reorganization of sympathetic efferent pathways to the **urinary bladder** of the cat following chronic unilateral, parasympathetic preganglionic denervation of the **bladder.** 2. Electrical stimulation (10-30 Hz) of the hypogastric nerve in cats with an intact **bladder** innervation or on the normally innervated side of the **bladder** in unilaterally denervated preparations elicited low-amplitude (10-25 cmH2O) transient (10-30 s) **bladder** contractions and non synaptic axonal volleys on **bladder** postganglionic nerves. However, after chronic (3-22 months) sacral preganglionic denervation, hypogastric nerve stimulation on the side of the denervation elicited large (60-80 cmH2O) and more sustained (4 5 min) **bladder** contractions as well as synaptically mediated firing on **bladder** postganglionic nerves. 3. The vesicoexcitatory effects of hypogastric nerve stimulation on the chronically denervated side were not altered selectively by the adrenergic blocking agent, phenoxybenzamine, but were blocked by atropine and hexamethonium suggesting that the responses were mediated by **muscarinic** and nicotinic cholinergic synapses. These drugs did not influence the responses elicited by hypogastric nerve stimulation on the normally innervated side of the **bladder.** 4. Following more extensive chronic unilateral denervation (transection of the pelvic and hypogastric nerves on one side of the **bladder**) stimulation of the contralateral intact pelvic nerve elicited postganglionic firing in vesical postganglionic nerves on the denervated side. This crossed excitatory pathway was not observed in normal animals or following sacral preganglionic denervation. 5. It is concluded that parasympathetic preganglionic denervation of the **bladder** ganglia leads to a reinnervation of the denervated cholinergic ganglion cells by sympathetic preganglionic pathways in the ipsilateral hypogastric nerve. This reinnervation results in the conversion of sympathetic **inhibitory** pathways to excitatory pathways in the denervated **bladder.** This change may contribute to the development of the autonomous hyperactive **bladder** seen under conditions of peripheral nerve or conus medullaris lesions of the spinal cord.

L12 ANSWER 79 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90017077 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2477832
TITLE: Contractile properties of human prostate adenomas and the development of infravesical obstruction.
AUTHOR: Gup D I; Shapiro E; Baumann M; Lepor H
CORPORATE SOURCE: Division of Urologic Surgery, Jewish Hospital of St. Louis, MO 63110.
CONTRACT NUMBER: RR05491-25 (NCRR)
SOURCE: Prostate, (1989) 15 (2) 105-14.
Journal code: 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198911
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19891114

AB The contractile response of human prostate adenomas to KCl, phenylephrine (alpha 1 adrenergic agonist), UK 14304 (alpha 2 adrenergic agonist), and carbachol (**muscarinic** cholinergic agonist) was evaluated in tissue specimens obtained from men with symptomatic and asymptomatic BPH. Prostate specimens were obtained from 5 men with asymptomatic BPH undergoing cystoprostatectomy, 11 men with symptomatic BPH undergoing open prostatectomy, and 11 men with symptomatic BPH undergoing transurethral resection of the prostate (TURP). Quantitative symptom score analysis and **urinary** flow rate determination documented the absence of **bladder** outlet obstruction in men undergoing cystoprostatectomy and confirmed the presence of **bladder** outlet obstruction in men undergoing prostatectomy. The magnitude of the contractile response (Emax) and the potency of phenylephrine induced contractions (EC50) in prostatic preparations obtained from men with symptomatic and asymptomatic BPH were similar. The IC50 for the **inhibition** of phenylephrine-induced contractions by prazosin was 3.2 nM, confirming that phenylephrine-induced contraction in the human prostate is mediated by the alpha 1 adrenoceptor. The contractile responses of prostate adenomas to **muscarinic** cholinergic and alpha 2 agonists were negligible. This study demonstrates that the development of **bladder** outlet obstruction in men with BPH is not related to alterations in the functional response of the smooth muscle component of the prostate adenoma.

L12 ANSWER 80 OF 121 MEDLINE on STN
ACCESSION NUMBER: 90015245 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2797217
TITLE: Prejunctional effects of **muscarinic** agonists on 3H-acetylcholine release in the rat **urinary bladder** strip.
AUTHOR: D'Agostino G; Chiari M C; Grana E
CORPORATE SOURCE: Institute of Pharmacology, Pavia, Italy.
SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (1989 Jul) 340 (1) 76-81.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198911
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19891108

AB The **inhibitory** effects of some **muscarinic** agonists on tritiated acetylcholine release evoked by field stimulation were investigated in the rat **urinary bladder** strip. The acetylcholine stores of the preparation were labelled with 3H choline. Electrical field stimulation caused an outflow of tritium, reflecting the release of 3H-acetylcholine. The release of 3H-acetylcholine was decreased in a concentration-dependent manner by all the agonists tested: oxotremorine, muscarone, muscarine, carbachol and methylfurtrethonium. On the contrary, only muscarine and muscarone enhanced the basal efflux of tritium in a concentration dependent fashion. Concentration-response curves were determined both at 2 Hz and at 1 Hz by using intermittent administration of the drugs. Maximal depression in release (by 78-82%) was observed in experiments at 1 Hz. A similar **inhibition** was obtained at 2 Hz frequency only when a low concentration of calcium (0.6 mM) in the medium was used. Oxotremorine was the most potent among the tested compounds with the same intrinsic activity as the other drugs. In contrast to the other agonists investigated, oxotremorine showed in about 10-fold greater potency at pre- than at postjunctional muscarine receptors in the rat **urinary bladder.** This difference might depend either on heterogeneity of muscarine receptors or on different mechanism(s) relating to the transducing properties of receptors at the pre- and postjunctional level. A comparison between the relative prejunctional potencies in the rat **urinary bladder** and in the guinea pig myenteric plexus (data from the literature) suggests that prejunctional muscarine receptors are similar in these tissues. Furthermore, the findings obtained with a low concentration of calcium in the medium may support the view that intraneuronal availability of calcium plays a significant role in modulating the prejunctional negative feed-back mechanism in the rat **urinary bladder.**

L12 ANSWER 81 OF 121 MEDLINE on STN
ACCESSION NUMBER: 89279738 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2543813
TITLE: **Muscarinic** receptors: relationships among phosphoinositide breakdown, adenylate cyclase **inhibition**, in vitro detrusor muscle contractions and in vivo cystometrogram studies in guinea pig **bladder.**
AUTHOR: Noronha-Blob L; Lowe V; Patton A; Canning B; Costello D; Kinnier W J
CORPORATE SOURCE: Nova Pharmaceutical Corporation, Baltimore, Maryland.
SOURCE: Journal of pharmacology and experimental therapeutics, (1989 Jun) 249 (3) 843-51.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19980206
Entered Medline: 19890721

AB The relationships between activation of **muscarinic** receptors in guinea pig **bladder** measured as carbachol stimulated inositol phosphate (IP) accumulation, oxotremorine-induced adenylate cyclase (AC) **inhibition** and **bladder** detrusor smooth muscle contraction determined in vitro as well as in vivo in the slow filling cystometrogram (CMG), were analyzed from the potencies of a number of **muscarinic** antagonists to block these responses. Significant positive linear correlations were found among the **inhibitory** potencies of 10 **muscarinic** antagonists to **inhibit** phosphoinositide (PI) turnover and both detrusor muscle contraction in vitro, as well as peak intravesical **bladder** pressure in vivo in the CMG (r = 0.8, P less than .01). In contrast, there was no significant correlation between the potency of antagonists to block the AC **inhibitory** response and either in vitro or in vivo guinea pig **bladder** contractions (P greater than .05). **Muscarinic** agonists **inhibited** basal AC activity to a maximum of 20% in a GTP-dependent, Na+-sensitive manner and dose dependently stimulated both PI breakdown (3- to 4 fold) and isolated detrusor contractions. Again, a significant correlation (r = 0.9, P less than .01) was calculated among the potencies of seven **muscarinic** agonists to elicit PI turnover and in vitro muscle contraction, whereas no significant correlation was observed between their potencies to **inhibit** AC activity and contractile responses in vitro. Collectively, the data suggest that IP accumulation and presumably IP-induced Ca++ release may function as the transducing mechanism for cholinergic contraction of the **urinary bladder.**(ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 82 OF 121 MEDLINE on STN
ACCESSION NUMBER: 89199462 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2539454
TITLE: Contractile responses in **bladder** body, **bladder** neck and prostate from rat, guinea pig and cat.
AUTHOR: Cohen M L; Drey K
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana.
SOURCE: Journal of pharmacology and experimental therapeutics, (1989 Mar) 248 (3) 1063-8.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198905
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890512

AB Lower **urinary** tract smooth muscle displays marked heterogeneity in pharmacologic responsiveness to contractile agents. The present study details differences among species with regard to **muscarinic,** adrenergic, histaminergic and serotonergic agonists in the **bladder** body, **bladder** neck and prostate from guinea pig, rat and cat. Under in vitro conditions, all smooth muscle preparations contracted to potassium chloride. The **muscarinic** agonist, carbamylcholine, produced maximal contraction, whereas alpha receptor agonists exerted only minimal, if any, effect in **bladder** body preparations from all three species. In contrast, alpha receptor-mediated responses predominated relative to **muscarinic** responses in **bladder** neck preparations from all three species. Prostatic contractility was examined in tissue from guinea pig and rat and contraction occurred to both alpha and **muscarinic** receptor agonists. Contractile response to norepinephrine in **bladder** neck and prostate was potentiated by neuronal uptake **inhibition** but not by beta receptor blockade. Serotonin and histamine exhibited more diverse effects among species and tissues. In general, histamine contracted all three tissues from guinea pig with minimal contraction occurring in tissues from rat or cat. On the other hand, serotonin markedly contracted the cat **bladder** body and rat prostate, but exerted no effect on tissues from the guinea pig. These data reinforce and detail the heterogeneity of pharmacologic contractile responses in lower **urinary** tract smooth muscle. Furthermore, the studies document the relative similarity among species in cholinergic and adrenergic responsiveness and the dissimilarity among species in serotonergic and histaminergic responsiveness of lower **urinary** tract smooth muscle.

L12 ANSWER 83 OF 121 MEDLINE on STN
ACCESSION NUMBER: 89150848 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3228673
TITLE: Mechanism of action of nicotine in isolated **urinary bladder** of guinea-pig.
AUTHOR: Hisayama T; Shinkai M; Takayanagi I; Toyoda T
CORPORATE SOURCE: Department of Chemical Pharmacology, Toho University School of Pharmaceutical Sciences, Chiba, Japan.
SOURCE: British journal of pharmacology, (1988 Oct) 95 (2) 465-72.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198904
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890413

AB 1. Nicotine produced a transient contraction of isolated strips of guinea-pig **urinary bladder.** The response to nicotine was antagonized by the nicotinic receptor antagonist, hexamethonium but was insensitive to tetrodotoxin. 2. The nicotine-induced contraction was potentiated by the **cholinesterase inhibitor,** physostigmine, and was reduced to 50% and 70% by the **muscarinic** cholinoceptor antagonist, atropine and the sympathetic neurone blocking drug, guanethidine, respectively. Chemical denervation with 6-hydroxydopamine abolished the **inhibitory** effect of guanethidine. Simultaneous treatment with atropine and guanethidine did not abolish the response to nicotine, but the degree of **inhibition** was comparable to that obtained with atropine alone. 3. The nicotine-induced contraction was insensitive to bunazosin and yohimbine (alpha 1 and alpha 2 adrenoceptor antagonists, respectively), and exogenously applied noradrenaline did not cause a contraction even in the presence of blockade of noradrenaline uptake mechanisms with desipramine and normetanephrine and of beta-adrenoceptors with propranolol, suggesting a non-adrenergic nature of the sympathomimetic effect of nicotine in this tissue. 4. The nicotine induced contraction in the presence of atropine was abolished after desensitization of P2-purinoceptors with alpha, beta-methylene adenosine 5'-triphosphate, a slowly degradable ATP analogue selective for P2-purinoceptors. By this desensitization, the response to ATP, but not to histamine, was also abolished. 5. A cyclo-oxygenase **inhibitor** flurbiprofen partially **inhibited** the nicotine-induced contraction. The degree of the **inhibition** was more pronounced in the presence of atropine than in its absence. Flurbiprofen antagonized the response to exogenously applied ATP in an unsurmountable manner, but not that to carbachol. (ABSTRACT TRUNCATED AT 250 WORDS)

L12 ANSWER 84 OF 121 MEDLINE on STN
ACCESSION NUMBER: 89094334 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2463333
TITLE: In vivo motor effects of substance P on the rat **urinary bladder.**
AUTHOR: Berggren A; Ahlman H; Dahlstrom A; Rubenson A; Sillen U
CORPORATE SOURCE: Department of Pediatric Surgery, East Hospital, Goteborg, Sweden.
SOURCE: Journal of neural transmission, (1988) 74 (3) 207-17.
Journal code: 0337042. ISSN: 0300-9564.
PUB. COUNTRY: Austria
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198902
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19960129
Entered Medline: 19890213

AB Intravesical pressure recordings of the **urinary bladder** in anesthetized rats were performed and the role of substance P (SP) in the motor control of this organ was evaluated. Regional injection of SP (0.4 nmoles i.a.) into the superior vesical artery elicited a prompt **bladder** contraction; this motor response was dosedependent. The detrusor contraction could be completely **inhibited** by a SP analogue, (D Pro2, D-Trp7,9)-SP (45-90 nmoles i.a.). Furthermore, the detrusor contraction evoked by preganglionic stimulation of the pelvic nerves was partially **inhibited** by the same antagonist in a higher dose (65% reduction at a total dose of 150-300 nmoles). The contractile response to SP (0.5 nmoles i.a.) was also significantly reduced after blockade of **muscarinic** receptors with atropine (50% reduction at 1 mg/kg i.a.) or after ganglionic blockade with hexamethonium (75% reduction at 25 mg/kg i.v. + 50 mg/kg hr i.a.). Immunocytochemical studies demonstrated the occurrence of SP-immunopositive nerve terminals in the detrusor part of the rat **urinary bladder.** Based on these findings it is suggested that SP may act as a neurotransmitter/modulator in this organ. The mechanism of action for SP on the detrusor seems to be complex and may involve ganglionic transmission via both types of cholinoceptors as well as direct activation of smooth muscle.

L12 ANSWER 85 OF 121 MEDLINE on STN
ACCESSION NUMBER: 89074918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2904773
TITLE: Regulation of [3H]GABA release from strips of guinea pig **urinary bladder.**
AUTHOR: Shirakawa J; Taniyama K; Iwai S; Tanaka C
CORPORATE SOURCE: Department of Anesthesiology, Kobe University, School of Medicine, Japan.
SOURCE: American journal of physiology, (1988 Dec) 255 (6 Pt 2) R888-93.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198901
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19950206
Entered Medline: 19890126

AB The presence of receptors that regulate the release of gamma-aminobutyric acid (GABA) was studied in strips of the guinea pig **urinary bladder.** GABA (10(-8)-10(-5) M) and muscimol (10(-8) 10(-5) M), but not baclofen (10(-5) M), reduced the Ca2+-dependent, tetrodotoxin-resistant release of [3H]GABA evoked by high K+ from the **urinary bladder** strips preloaded with [3H]GABA. The **inhibitory** effect of muscimol was antagonized by bicuculline and potentiated by diazepam, clonazepam, and pentobarbital sodium. The potentiating effect of clonazepam was antagonized by Ro 15-1788. Acetylcholine (ACh) **inhibited** the high K+-evoked release of [3H]GABA. The **inhibitory** effect of ACh was antagonized by atropine sulfate and pirenzepine but not by hexamethonium. Norepinephrine (NE) **inhibited** the evoked release of [3H]GABA. The **inhibitory** effect of NE was mimicked by clonidine, but not by phenylephrine, and was antagonized by yohimbine but not by prazosin. These results provide evidence that the release of GABA from strips of guinea pig **urinary bladder** is regulated via the bicuculline-sensitive GABAA receptor, M1-**muscarinic,** and alpha 2-adrenergic receptors.

L12 ANSWER 86 OF 121 MEDLINE on STN
ACCESSION NUMBER: 89014401 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3173349
TITLE: Dissociation of the metabolic from the contractile response to **muscarinic** stimulation in the rabbit **urinary bladder.**
AUTHOR: Ruggieri M R; Wein A J; Hypolite J A; Levin R M
CORPORATE SOURCE: Division of Urology, University of Pennsylvania School of Medicine, Philadelphia.
CONTRACT NUMBER: RO-1-DK 33559 (NIDDK)
RO-1-DK-2-6508 (NIDDK)
SOURCE: Molecular and cellular biochemistry, (1988 Jun) 81 (2) 137-43.
Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881121

AB The calcium dependence of contraction and NADH fluorescence was investigated in rabbit **bladder** stimulated with bethanechol or KCl. The absence of calcium in the bathing solution induced a rightward shift in the dose response to bethanechol for both contraction and NADH fluorescence. The contractile response was shifted to a greater degree than the fluorescence response and the maximal response to bethanechol was reduced by 80% for contraction but only 20% for NADH fluorescence. This rightward shift was also induced by the benzothiazepine calcium antagonist diltiazem (200 microM) and again the contractile response was shifted significantly more than the fluorescence response. The combination of zero calcium and 200 microM diltiazem virtually abolished contractions but only **inhibited** the NADH fluorescence by 65% at maximally effective bethanechol concentrations. Unlike the effect of diltiazem on the response to bethanechol, diltiazem (200 microM) shifted both the contraction and fluorescence curves to the right equally in response to KCl stimulation. These results indicate that a metabolic response to **muscarinic** stimulation (decreased NADH) can occur in the absence of any observable contractile response. This metabolic response may be due to post receptor signal processing events. For KCl stimulation, the NADH response is probably secondary to and a result of the contractile response.

L12 ANSWER 87 OF 121 MEDLINE on STN
ACCESSION NUMBER: 88273235 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3392052
TITLE: Differential effects of pertussis toxin on **muscarinic** responses in isolated atria and smooth muscle.
AUTHOR: Eglen R M; Huff M M; Montgomery W W; Whiting R L
CORPORATE SOURCE: Institute of Pharmacology, Syntex Research, Palo Alto, California 94303.
SOURCE: Journal of autonomic pharmacology, (1988 Mar) 8 (1) 29 37. Journal code: 8106455. ISSN: 0144-1795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198808
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 20021218
Entered Medline: 19880817

AB 1. The effect of pretreatment with pertussis toxin has been studied on responses to **muscarinic** agonists in guinea-pig atria and smooth muscle in vitro. 2. 48 h after a single intravenous injection of pertussis toxin (3.2-100 micrograms.kg-1), **muscarinic** receptor-mediated negative inotropic responses in the atria were **inhibited** in a dose-dependent manner, with complete abolition of responses occurring after administration of 100 micrograms.kg-1. 3. In contrast, there was no effect on atrial positive inotropic responses to isoprenaline. In addition, no effect was observed on contractile responses to carbachol and pilocarpine in the ileum, trachea, oesophageal muscularis mucosae and **urinary bladder**, either in terms of potency or maximal response, at all dose levels of pertussis toxin studied. 4. It is concluded that **muscarinic** receptors in the atria, but not smooth muscle, are probably coupled to the **inhibitory** regulatory protein Ni, which is functionally inactivated by pertussis toxin. The differences in coupling between atrial and smooth muscle **muscarinic** receptors provide further evidence for **muscarinic** receptor heterogeneity in these two tissues.

L12 ANSWER 88 OF 121 MEDLINE on STN
ACCESSION NUMBER: 88251531 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2838033
TITLE: Pharmacological activities of the main metabolite of flavoxate 3-methylflavone-8-carboxylic acid.
AUTHOR: Cazzulani P; Pietra C; Abbiati G A; Ceserani R; Oliva D; Civelli M; Tajana A; Nardi D
CORPORATE SOURCE: Research Division, Recordati S.p.a., Milan, Italy.
SOURCE: Arzneimittel-Forschung, (1988 Mar) 38 (3) 379-82. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880720

AB The pharmacological properties of 3-methylflavone-8-carboxylic acid (MFCA), the main metabolite of flavoxate, have been studied in vitro and in vivo. MFCA did not display antispasmodic activity on isolated organs contractions induced by histamine, acetylcholine or CaCl2, nor did it exhibit significant affinity for the rat brain alpha- and beta-adrenergic, serotoninic, **muscarinic**, D2, opiate and Ca2+ receptors. However, it showed a remarkable phosphodiesterase (PDE) **inhibiting** activity. Moreover in vivo studies indicate an interesting activity of MFCA which **inhibited** the rat **urinary bladder** voiding contractions, increased **bladder** volume capacity and decreased micturition pressure in the rat cystometric recordings. The activity of MFCA in the two in vivo experimental models, probably related to cAMP-PDE **inhibitory** properties, suggests that flavoxate's therapeutical potential might be partially sustained by its main metabolite.

L12 ANSWER 89 OF 121 MEDLINE on STN
ACCESSION NUMBER: 88242686 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3378565
TITLE: Characterization of the **muscarinic** receptor subtypes in the rat **urinary bladder.**
AUTHOR: Monferini E; Giraldo E; Ladinsky H
CORPORATE SOURCE: Department of Biochemistry, Istituto De Angeli S.p.A., Milan, Italy.
SOURCE: European journal of pharmacology, (1988 Mar 15) 147 (3) 453-8. Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880725

AB We investigated the nature of the **muscarinic** receptors present in the rat **urinary bladder** by performing binding studies with various selective (pirenzepine, AF-DX 116, hexahydrosiladifenidol, benzhexol, 4-diphenyl-acetoxy N-methyl piperidine methiodide, dicyclomine, secoverine) and classical (N-methylscopolamine, atropine) antagonists. Competition experiments were carried out against [3H]N-methyl scopolamine at 30 degrees C in Na+/Mg2+ HEPES buffer; non-specific binding was determined in the presence of 1 microM 3-quinuclidinyl benzilate. Of all the antagonists examined, only AF-DX 116 exhibited a heterogeneous binding profile (nH less than 1). Computer-assisted analysis showed that the data fitted best to a two-binding site model, revealing the existence of high and low affinity receptors. The affinity values of AF-DX 116, determined in binding experiments carried out in heart and gland homogenates, allowed us to classify the rat **urinary bladder** receptors into cardiac and glandular subtypes. We suggest that the glandular receptor subtype is involved in smooth muscle contraction, since AF-DX 116 was equally potent in **inhibiting** smooth muscle contraction and the secretion of saliva.

L12 ANSWER 90 OF 121 MEDLINE on STN
ACCESSION NUMBER: 88172688 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2832620
TITLE: Identification of receptor subtypes in the rabbit and human **urinary bladder** by selective radio-ligand binding.
AUTHOR: Levin R M; Ruggieri M R; Wein A J
CORPORATE SOURCE: Division of Urology, University of Pennsylvania School of Medicine, Philadelphia.
CONTRACT NUMBER: RO-1-DK 33559 (NIDDK)
RO-1-DK-2-6508 (NIDDK)
SOURCE: Journal of urology, (1988 Apr) 139 (4) 844-8. Journal code: 0376374. ISSN: 0022 5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198804
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880429

AB Recent advances in receptor technology have demonstrated that subtypes of each autonomic receptor exist. Using both direct radio-ligand studies and the **inhibition** of receptor binding by subtype-selective pharmacological antagonists, we have studied the distribution of subtypes of alpha and beta adrenergic receptors and **muscarinic** cholinergic receptors in the **urinary bladder** of the rabbit and man. Alpha adrenergic receptors were quantified by direct binding of tritiated prazosin (alpha-1), yohimbine (alpha-2), and the non-selective alpha adrenergic ligand dihydroergocriptine (DHE). These studies demonstrated that the distribution of alpha receptor subtypes in the **bladder** base (for both rabbit and human) is approximately 80% alpha-1 and 20% alpha-2. Beta receptor subtypes were identified by the **inhibition** of the non-selective ligand 3H-dihydroalprenalol (DHA) by the beta-1 selective **inhibitor** ICI 89 and the beta-2 selective **inhibitor** ICI-118. Initial studies demonstrated that the beta adrenergic density of the **bladder** body was 92 fmol per mg. protein for the rabbit and 32 fmol per mg. protein for human **bladder** body. **Inhibition** of DHA binding by ICI-118 demonstrated a single class of receptor with an IC50 of approximately 0.013 microM for both rabbit and human. **Inhibition** of DHA binding by ICI-89 also demonstrated one class of receptors with an IC50 of approximately 9.0 microM for both species. These results indicate that there are primarily beta-2 receptors in the rabbit and human **bladder** body. Although the number of **muscarinic** subtypes in existence is currently being re-evaluated, there are at least two which can be identified by the selective **muscarinic** agent pirenzepine (PZP). The brain has been shown to contain both high and low affinity PZP sites. Using both direct PZP binding to the **bladder** body, and the **inhibition** by PZP of the non-selective radio-ligand quinuclidinyl benzylate (QNB), we have demonstrated that both the rabbit and human **bladder** body have no observable high affinity PZP-selective binding and the **inhibition** of 3H-QNB by PZP demonstrated that there was only the low-affinity PZP binding site. Although receptor subtypes in the **bladder** have been the subject of numerous investigations, this is the first study describing the distribution of both adrenergic and cholinergic receptor subtypes in both the rabbit and human.

L12 ANSWER 91 OF 121 MEDLINE on STN
ACCESSION NUMBER: 88034192 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3668160
TITLE: Identification and characterization of **muscarinic** cholinergic receptors in the human **urinary bladder** and parotid gland.
COMMENT: Erratum in: J Auton Nerv Syst 1988 Mar;22(2):174. Bjorklund A[corrected to Biorklund A]
AUTHOR: Batra S; Biorklund A; Hedlund H; Andersson K E; Bjorklund A
CORPORATE SOURCE: AB Leo Research Laboratories, Helsingborg, Sweden.
SOURCE: Journal of the autonomic nervous system, (1987 Aug) 20 (2) 129-35.
Journal code: 8003419. ISSN: 0165-1838.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198711
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871130

AB The binding characteristics of [3H]quinuclidinyl benzilate (QNB) to **muscarinic** sites in isolated plasma membrane fractions of the human **urinary bladder** and parotid gland were studied. QNB binding to both preparations was of high affinity and low capacity. Mean values for the apparent dissociation constants (Kd) for binding to membrane preparations from the **urinary bladder** and parotid glands were 22 and 34 pM and the Bmax values 234 and 456 fmol/mg protein, respectively. Significance of difference between Kd and Bmax values from the two tissues was at the level of P less than 0.005 and P less than 0.05, respectively. QNB binding was **inhibited** by **muscarinic** receptor antagonists with varying degree of effectiveness. The mean values for the **inhibition** constant (Ki) were significantly lower for oxybutynin, amitriptyline, and pirenzepine but higher for secoverine in preparations of the **urinary bladder** than of the parotid gland. The mean Ki values for quinidine and verapamil were lower in the **urinary bladder** than that in the parotid gland. Carbachol exhibited a marked selectivity for the **urinary bladder** (about 30-fold) compared with the parotid gland. The present data obtained in two human tissues that are highly cholinergic in their innervation give support to the argument for heterogeneity of the **muscarinic** cholinergic receptors.

L12 ANSWER 92 OF 121 MEDLINE on STN
ACCESSION NUMBER: 87322496 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3630733
TITLE: Source of calcium for contractions induced by depolarization and **muscarinic** receptor stimulation in rabbit **urinary bladder.**
AUTHOR: Batra S; Sjogren C; Andersson K E; Fovaeus M
SOURCE: Acta physiologica Scandinavica, (1987 Aug) 130 (4) 545-51.
Journal code: 0370362. ISSN: 0001-6772.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198710
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871014

AB Omission of calcium or the inclusion of lanthanum in the bathing medium resulted in an almost complete **inhibition** of contractile responses induced by either K+ depolarization or carbachol in strips of rabbit **urinary bladder.** D-600 **inhibited** K+-induced contractions significantly more than carbachol-induced responses. The influx of 45Ca into cells was stimulated both by K+ depolarization and carbachol. Over a 2-min period the increase in 45Ca influx induced by high K+ and carbachol was 98 and 65%, respectively. Both lanthanum and D-600 blocked 45Ca influx stimulated by either K+ depolarization or carbachol. The **inhibition** of 45Ca influx by these calcium-channel blocking agents, particularly by D-600, was dependent on the length of exposure. Application of carbachol during 45Ca efflux in pre-loaded muscle strips had no effect on the rate of 45Ca efflux. These results indicate that the contractile responses of the **urinary bladder** to depolarization and to carbachol are highly dependent on an extracellular source of calcium.

L12 ANSWER 93 OF 121 MEDLINE on STN
ACCESSION NUMBER: 87304487 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3622609
TITLE: Comparison of **muscarinic** acetylcholine binding in the **urinary bladder** and submandibular gland of the rabbit.
AUTHOR: Batra S
SOURCE: European journal of pharmacology, (1987 Jun 12) 138 (1) 83-8.
Journal code: 1254354. ISSN: 0014 2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198710
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19871016

AB In order to explore the possibility of heterogeneity in peripheral muscarine receptors, receptors were characterized in membrane fractions isolated from rabbit **urinary bladder** and submandibular gland. With [3H]QNB as radioligand, specific binding with very high affinity was found in both preparations. Although the BmaxS for binding in the two preparations were very similar, the mean KD value in the submandibular gland was significantly higher (P less than 0.005) than that in the **bladder.** Among the anticholinergic drugs, oxybutynin had a significantly lower value for the **inhibition** constant (Ki) in the submandibular gland whereas Ki for both secoverine and pirenzepine was significantly higher in this tissue than in **urinary bladder.** The Ki for carbacholine was about 7-fold higher in submandibular gland than in the **bladder.** Although quinidine and verapamil showed relatively weak binding to the muscarine receptor site, their Ki in the submandibular gland was significantly higher than that in the **bladder.** The results indicate that although there is a considerable similarity between **muscarinic** receptors in **urinary bladder** and submandibular gland, the differences in Ki values for different compounds in the two tissues support the argument favouring heterogeneity of **muscarinic** acetylcholine receptors in peripheral effector organs.

L12 ANSWER 94 OF 121 MEDLINE on STN
ACCESSION NUMBER: 87198978 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3573166
TITLE: Interaction between adrenergic and cholinergic nerve terminals in the **urinary bladder** of rabbit, cat and man.
AUTHOR: Mattiasson A; Andersson K E; Elbadawi A; Morgan E; Sjogren C
SOURCE: Journal of urology, (1987 May) 137 (5) 1017-9.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198706
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19900303
Entered Medline: 19870601

AB The influence of **muscarinic** receptor stimulation (carbachol) and blockade (scopolamine) on the release of 3H-labelled noradrenaline from adrenergic neurons was investigated in isolated detrusor preparations from rabbit, cat and man. A significant influence on the release of 3H from adrenergic nerve terminals was found in the three species with a concentration-dependent decrease and increase induced by carbachol and scopolamine, respectively. Using the alpha 2-adrenoceptor stimulating and blocking agents clonidine and rauwolscine in rabbit and human detrusor preparations, the presence of prejunctionally located **inhibitory** alpha 2-adrenoceptors could also be demonstrated. The findings indicate the possibility of a functionally important interaction between cholinergic and adrenergic nerves in the **urinary bladder** mediated via **inhibitory muscarinic** receptors on adrenergic nerve terminals.

L12 ANSWER 95 OF 121 MEDLINE on STN
ACCESSION NUMBER: 87144723 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2434871
TITLE: Prostanoid synthesis by the rat **urinary bladder**: evidence for stimulation through muscarine receptor-linked calcium channels.
AUTHOR: Jeremy J Y; Mikhailidis D P; Dandona P
SOURCE: Naunyn-Schmiedeberg's archives of pharmacology, (1986 Dec) 334 (4) 463 7.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19900303
Entered Medline: 19870420

AB An in vitro model for the study of muscarine receptor-mediated synthesis of prostacyclin (PGI2) and other prostanoids (PGE2 and PGF2 alpha) by the rat **urinary bladder** is described. PGI2 synthesis was stimulated by parasympathomimetic agents (carbachol greater than methacholine greater than arecoline; McNA 343, nicotine and dimethyl phenyl piperazinium were without effect). Methacholine (3 X 10(-6) mol X l-1)-stimulated PGI2 synthesis was **inhibited** by **muscarinic** antagonists (atropine greater than ipratroprium bromide greater than gallamine greater than pirenzepine) and was completely abolished by the presence of ethylene diamine tetraacetic acid (EDTA: 10 mmol X l l). Verapamil also **inhibited** methacholine-stimulated PGI2 synthesis in a dose-dependent manner. The antagonistic action of atropine was shown to be competitive, but had no effect on calcium ionophore A23187-stimulated PGI2 synthesis. High concentrations of [K+] (up to 0.11 mol X l-1) were without effect on PGI2 synthesis. PGE2, PGF2 alpha and PGI2 synthesis were all equally stimulated with methacholine, carbachol, arecoline and A23187, and methacholine-stimulated synthesis of these prostanoids was equally **inhibited** by atropine, ipratroprium bromide, gallamine, verapamil and EDTA. It is concluded that in vitro prostanoid synthesis by the rat **urinary bladder** : is stimulated by post ganglionic muscarine receptors; involves a muscarine receptor-linked calcium influx system; and is mediated by a predominance of M2 subtype receptors.

L12 ANSWER 96 OF 121 MEDLINE on STN
ACCESSION NUMBER: 87112359 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3806496
TITLE: Identification and characterization of **muscarinic** cholinergic receptors in the isolated plasma membranes and intact tissue of the **urinary bladder.**
AUTHOR: Batra S
SOURCE: Journal of receptor research, (1986) 6 (3-4) 227-46.
Journal code: 8008358. ISSN: 0197-5110.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198702
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870224

AB The binding characteristics of 3H-quinuclidinyl benzilate (QNB) to strips of intact tissue and to isolated plasma membrane fraction (PM) from rabbit **urinary bladder** were studied. QNB binding to both preparations was of high affinity and low capacity. The equilibrium dissociation constants (KD) for binding to tissue strips and PM were 2.2 and 0.045 nM respectively. **Muscarinic** antagonists **inhibited** QNB binding more effectively than agonists. Ca-antagonist D-600, but not nifedipine caused an **inhibition** of QNB binding to PM. Vanadate, ouabain or N-ethylmelaimide had no significant effect on QNB binding. In contrast to the binding in PM, binding in the intact tissue was reduced by K-depolarization.

L12 ANSWER 97 OF 121 MEDLINE on STN
ACCESSION NUMBER: 87036443 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3772807
TITLE: Presynaptic **inhibitory muscarinic** receptors modulating [3H] acetylcholine release in the rat **urinary bladder.**
AUTHOR: D'Agostino G; Kilbinger H; Chiari M C; Grana E
SOURCE: Journal of pharmacology and experimental therapeutics, (1986 Nov) 239 (2) 522-8.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198612
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19861211

AB The occurrence of presynaptic **muscarinic** receptors **inhibiting** the release of acetylcholine (ACh) from nerve terminals was investigated in the rat **urinary bladder.** Strips from the extratrigonal area were preincubated with [3H]choline and stimulated at 0.2 Hz. Both [3H]ACh and [3H]choline content were measured in the tissue. The uptake of tritiated choline was prevented by hemicholinium 3. The field stimulation at 2 Hz (360 shocks) produced a release of tritium. Most of the induced outflow was found to be [3H]ACh. Both tetrodotoxin treatment and calcium omission from the medium prevented such an evoked outflow of tritium. When two electrical stimulations (S1 and S2) at 2 Hz (360 shocks) were carried out at 45-min intervals, an S2/S1 ratio of 0.82 was found. Physostigmine reduced the evoked-release of [3H]ACh whereas atropine increased it in a concentration-dependent manner. Atropine antagonized the **inhibitory** effect of physostigmine, so that the S2/S1 ratio did not vary significantly from control experiments. Both carbachol and muscarine strongly decreased the [3H]ACh evoked outflow. Muscarine increased the spontaneous outflow of tritium also. These findings suggest that the **urinary bladder** of the rat is equipped with presynaptic **inhibitory muscarinic** receptors modulating ACh release from cholinergic postganglionic neurons.

L12 ANSWER 98 OF 121 MEDLINE on STN
ACCESSION NUMBER: 86282009 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3755479
TITLE: Action of pirenzepine on the human **urinary bladder** in vitro.
AUTHOR: Zappia L; Cartella A; Potenzoni D; Bertaccini G
SOURCE: Journal of urology, (1986 Sep) 136 (3) 739-42.
Journal code: 0376374. ISSN: 0022 5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860925

AB The novel compound pirenzepine was tested for its antimuscarinic effect on the human **urinary bladder** "in vitro." Its behavior towards the contractions induced by acetylcholine or bethanechol and towards electrically induced contractions was identical to that of atropine. However, its potency was 100 to 300 times lower than that of atropine. Results obtained with ganglion blocking agents, tetrodotoxin and cooled preparations of **urinary bladder** seem to indicate the virtually total absence of ganglionic cells. On the other hand they point out the fundamental role of post-synaptic **muscarinic** M2 receptors as the most important component of the cholinergic system in the **bladder.** Of course the existence of other transmitters released at the cholinergic nerve endings after electrical field stimulation cannot be excluded on the basis of our experiments.

L12 ANSWER 99 OF 121 MEDLINE on STN
ACCESSION NUMBER: 86034034 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2414301
TITLE: Characterization of cholinoreceptors in the rat **urinary bladder** by the use of agonists and antagonists of the cholinergic system.
AUTHOR: Adami M; Bertaccini G; Coruzzi G; Poli E
SOURCE: Journal of autonomic pharmacology, (1985 Sep) 5 (3) 197-205.
Journal code: 8106455. ISSN: 0144-1795.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198512
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19950206
Entered Medline: 19851210

AB The effects of stimulatory and **inhibitory** compounds acting on both nicotinic and **muscarinic** receptors have been evaluated in the isolated **urinary bladder** from adult and immature (14-18 days old) rats. Acetylcholine and bethanechol were found to induce concentration-dependent contractions which were **inhibited** by atropine and pirenzepine; compound McN-A-343 had a negligible contractile activity whereas DMPP had no effect at all. Responses to electrical field stimulation were abolished by tetrodotoxin (3 X 10(-8) M), enhanced by eserine (10(-8) M) and scarcely affected by hexamethonium (10(-3) M), trimethaphan (10(-3) M) and d-tubocurarine (10(-3) M). Atropine, pirenzepine and DMPP induced only a partial **inhibition** (50%) of the twitch response, whereas compound McN-A 343 caused a concentration-dependent **inhibitory** effect which was maximum (100% **inhibition**) at 10(-2) M. No significant differences were found between results obtained in immature and adult animals as regards either the stimulatory or the **inhibitory** compounds tested. It was concluded that postjunctional **muscarinic** receptors were responsible for the stimulatory responses observed, whereas an additional involvement of unknown mechanisms, probably not related to the cholinergic system, was suggested by the peculiar results obtained with DMPP and compound McN-A-343 on electrically-stimulated **urinary bladder**. Whatever the mechanisms involved, however, they are already present at the first stage of postnatal development.

L12 ANSWER 100 OF 121 MEDLINE on STN
ACCESSION NUMBER: 85285317 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4029260
TITLE: Pharmacological evidence for selective **inhibition** of gastric acid secretion by telenzepine, a new antimuscarinic drug.
AUTHOR: Eltze M; Gonne S; Riedel R; Schlotke B; Schudt C; Simon W A
SOURCE: European journal of pharmacology, (1985 Jun 7) 112 (2) 211-24.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198510
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19851009

AB The new antisecretory drug, telenzepine (4,9-dihydro-3-methyl-4-[(4-methyl-1-piperazinyl)acetyl]-10H-thieno-[3,4 - b][1,5]benzodiazepin-10-one), was investigated for its **inhibition** of functionally intact **muscarinic** receptors involved in gastric acid secretion in rabbit fundic glands, perfused mouse stomach in vitro, perfused rat stomach in situ, gastric fistula in rats and dogs with a Heidenhain pouch. The effects on these receptors were contrasted with effects on receptors located on smooth muscle and heart, i.e. isolated rat **urinary bladder**, stomach and atrium. The results were compared to those values obtained with nonselective antimuscarinic drugs (N-methylscopolamine, atropine) and the selective M-1 antagonist pirenzepine. Telenzepine was found to be 4-10 times more potent than pirenzepine with respect to depressing both gastric acid secretion and smooth muscle or myocardial responses. Based on -log EC50 and pA2 values, both drugs exhibited a similar selectivity profile differing from the pattern of effects observed with atropine or a second reference compound, zolenzepine. As compared with atropine, telenzepine exhibited a 5 fold higher relative affinity to **muscarinic** receptors involved in gastric acid secretion. It was concluded that telenzepine is selective to discriminate between **muscarinic** receptors mediating gastric acid secretion and affecting muscle contractility and that this finding supports the concept of **muscarinic** receptor heterogeneity.

L12 ANSWER 101 OF 121 MEDLINE on STN
ACCESSION NUMBER: 85058429 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2981104
TITLE: Effects of vasoactive intestinal polypeptide on isolated urethral and **urinary bladder** smooth muscle from rabbit and man.
AUTHOR: Sjogren C; Andersson K E; Mattiasson A
SOURCE: Journal of urology, (1985 Jan) 133 (1) 136-40.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198501
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850124

AB Vasoactive intestinal polypeptide concentration-dependently **inhibited** the contractant responses of isolated preparations of the female rabbit **bladder** and urethra induced by electrical field stimulation and exogenous application of acetylcholine (**bladder**) and noradrenaline (urethra). The **inhibition** of alpha-adrenoceptor and **muscarinic** cholinoceptor-mediated activity in the urethra and **bladder** amounted to 50 to 90 per cent of induced contractions. The nonadrenergic noncholinergic contraction induced by electrical field stimulation in the urethra was reduced slightly, whereas corresponding response in the **bladder** was more sensitive. The maximum **inhibition** of both the electrically induced responses and contractions induced by exogenous noradrenaline and acetylcholine was of comparable size in the urethra and the **bladder**. The effects of vasoactive intestinal polypeptide seemed to be exerted postjunctionally since no significant influence of the peptide was seen on the release of 3H-noradrenaline from adrenergic nerve endings in the urethra. The effects of vasoactive intestinal polypeptide in human urethral and **bladder** preparations were less consistent. The noradrenaline-induced contraction in urethral preparations was **inhibited** by 29 +/- 9 per cent (number = 22). The effects on electrically induced contractions in the urethra, and on responses to acetylcholine and electrical field stimulation in the **bladder**, were small and inconsistent. It is concluded that vasoactive intestinal polypeptide may be of importance for regulation of lower **urinary** tract smooth muscle activity in the rabbit. It cannot be excluded that the peptide has a modulatory role in neurotransmission in human urethral muscle. However, the present results do not support the view of vasoactive intestinal polypeptide as an **inhibitor** of contraction in human detrusor.

L12 ANSWER 102 OF 121 MEDLINE on STN
ACCESSION NUMBER: 84076350 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6650180
TITLE: Differences between binding affinities of some antimuscarinic drugs in the parotid gland and those in the **urinary bladder** and ileum.
AUTHOR: Nilvebrant L; Sparf B
SOURCE: Acta pharmacologica et toxicologica, (1983 Oct) 53 (4) 304-13.
Journal code: 0370572. ISSN: 0001-6683.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198401
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19840107

AB Possible differences between the **muscarinic** receptors in the guinea pig **urinary bladder** and those in the ileum and the parotid gland were investigated, using a receptor binding technique. The affinities of 18 antimuscarinic drugs were indirectly derived from the ability to **inhibit** the receptor-specific binding of the radioligand (-)3H-QNB. The Hill coefficients were close to unity which indicated that the drugs were bound to apparently uniform populations of receptors within each tissue. In contrast to traditional **muscarinic** antagonists, four drugs - namely, oxybutynine, dicyclomine, benzhexol and pirenzepine - bound with a significantly higher affinity in the parotid gland than in the **urinary bladder** and ileum. A tendency towards reversed selectivity was found for secoverine. Thus, the present results further support the hypothesis that differences in **muscarinic** receptors between tissues exist, e.g. smooth muscle compared with parotid gland, which can be detected only by certain antimuscarinic drugs.

L12 ANSWER 103 OF 121 MEDLINE on STN
ACCESSION NUMBER: 83268298 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6308243
TITLE: Electrical and mechanical activity recorded from rabbit **urinary bladder** in response to nerve stimulation.
AUTHOR: Creed K E; Ishikawa S; Ito Y
SOURCE: Journal of physiology, (1983 May) 338 149-64. Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198309
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19830923

AB Responses of the smooth muscle membrane of the rabbit **bladder** to intramuscular nerve stimulation were investigated by the micro-electrode and double sucrose-gap methods. The cell generated regular spontaneous action potentials. Acetylcholine produced a maintained increase in the frequency and ATP a transient increase. Noradrenaline only increased the frequency at very high concentrations. Application of short current pulses (50 microseconds) produced an initial excitatory junction potential (e.j.p.) with a superimposed spike, followed by a late depolarization. On some occasions, hyperpolarization of the membrane appeared between initial e.j.p. and the late depolarization. All these responses were abolished by tetrodotoxin. The late depolarization was enhanced by pre-treatment with neostigmine and abolished by atropine. This means that the delayed depolarization is due to activation of the **muscarinic** receptor. When the late depolarization was abolished, the amplitude of hyperpolarization was enhanced. The e.j.p. and contraction were unaffected by guanethidine, phentolamine, methysergide, mepyramine, quinidine or theophylline. This means that the e.j.p. is not mediated by activation of adrenergic, tryptaminergic, histaminergic or purinergic receptors. ATP reduced the amplitude of the e.j.p. due to depolarization of the membrane and reduction in the membrane resistance. The amplitude of the e.j.p. was gradually reduced by repetitive stimulation (0.5-2.0 Hz). However, the rate of depression was unchanged in the presence of ATP. Dipyridamole did not change the electrical and mechanical responses to field stimulation. These results do not support the proposal that ATP is the non-cholinergic excitatory transmitter. Apamine and tetraethylammonium (TEA) suppressed the hyperpolarization produced by field stimulation but guanethidine did not **inhibit** the hyperpolarization. Therefore, the hyperpolarization is due to increased K conductance of the membrane but it is not possible to conclude whether this component is due to the **inhibitory** action of a neurotransmitter or solely to after hyperpolarization of the spike. It was concluded that the rabbit **bladder** receives both cholinergic and noncholinergic excitatory neurones.

L12 ANSWER 104 OF 121 MEDLINE on STN
ACCESSION NUMBER: 83268141 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6875862
TITLE: Correlation between **cholinesterase inhibition** and reduction in **muscarinic** receptors and choline uptake by repeated diisopropylfluorophosphate administration: antagonism by physostigmine and atropine.
AUTHOR: Yamada S; Isogai M; Okudaira H; Hayashi E
SOURCE: Journal of pharmacology and experimental therapeutics, (1983 Aug) 226 (2) 519-25. Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198309
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19830920

AB **Muscarinic** receptors, [14C]choline uptake and acetylcholinesterase (AChE) activity in central and peripheral tissues of guinea-pigs treated repeatedly with diisopropylfluorophosphate (DFP) were simultaneously determined. After repeated DFP (1 mg/kg) administration, there was a significant decrease in specific [3H] quinuclidinyl benzilate binding only in the striatum, ileal longitudinal muscle and **urinary bladder** among various tissues examined. Scatchard analysis revealed that the administration of DFP at 0.5, 1 and 2 mg/kg which depressed the tissue AChE by 50 to 90%, caused a dose dependent decrease (20-50%) in striatal and ileal [3H]quinuclidinyl benzilate binding sites without a change in the dissociation constant. The lower dose (0.2 mg/kg) of DFP depressed significantly the AChE in both tissues by 30% but failed to alter their [3H]quinuclidinyl benzilate binding sites. High affinity uptake of [14C]choline in the striatum and ileal longitudinal muscle was significantly decreased by repeated administration of DFP at 0.5 and 1 mg/kg but not 0.2 mg/kg. The DFP-induced loss of striatal and ileal **muscarinic** receptors was effectively antagonized by a concomitant administration of physostigmine (0.5 mg/kg) and atropine (5 mg/kg). Also, these drugs antagonized the DFP-induced decrease in the striatal [14C]choline uptake. Thus, the present study has demonstrated that repeated DFP administration causes a specific decrease in **muscarinic** receptors and [14C]choline uptake in the striatum and ileal longitudinal muscle of guinea pigs which is closely associated with a considerable (more than 50%) depression of the tissue AChE. In addition, these adaptive changes by DFP were effectively antagonized by physostigmine and atropine.

L12 ANSWER 105 OF 121 MEDLINE on STN
ACCESSION NUMBER: 83174804 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6837322
TITLE: **Muscarinic** receptor binding in the guinea pig **urinary bladder.**
AUTHOR: Nilvebrant L; Sparf B
SOURCE: Acta pharmacologica et toxicologica, (1983 Jan) 52 (1) 30-8. Journal code: 0370572. ISSN: 0001 6683.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198305
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830505

AB The **muscarinic** receptors in the guinea pig **urinary bladder** and the longitudinal muscle of the guinea pig ileum were studied by means of a receptor-binding technique. l-Quinuclidinyl [phenyl 4-3H]benzilate ((-)3H-QNB) was employed as radio-ligand and the separation of bound from free (-) 3H-QNB was performed by microcentrifugation. Under conditions of equilibrium (-)3H-QNB was specifically bound with high affinity to a limited number of sites, 0.32 and 1.62 pmol/mg protein in the **bladder** and ileum, respectively. The binding appeared to represent a single population of non-interacting binding sites. The apparent dissociation constants were 2.6 x 10(-10) M in the **bladder** and 1.2 x 10(-9) M in the ileum, whereas the KD-values, estimated by extrapolation to an infinitely low receptor concentration were 1.1 x 10(-10) M (**bladder**) and 3.1 x 10(-10) M (ileum). The binding of (-)3H-QNB appears to represent an interaction with **muscarinic** receptors, as it was effectively **inhibited** by **muscarinic** antagonists and agonists, but not by a variety of non-cholinergic drugs.

L12 ANSWER 106 OF 121 MEDLINE on STN
ACCESSION NUMBER: 83147502 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7164219
TITLE: Central cholinergic mechanisms in L DOPA induced hyperactive **urinary bladder** of the rat.
AUTHOR: Sillen U; Rubenson A; Hjalmas K
SOURCE: Urological research, (1982) 10 (5) 239 43. Journal code: 0364311. ISSN: 0300-5623.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198304
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19980206
Entered Medline: 19830407

AB The involvement of central and peripheral cholinergic structures in the mediation of a centrally induced hyperactive **urinary bladder** response to L-2,3-dihydroxyphenylalanine (L-DOPA), after peripheral decarboxylase **inhibition**, registered by a cystometric procedure, has been analysed pharmacologically in anaesthetised rats. The **urinary bladder** response to L-DOPA was unchanged after blockade of cholinergic receptors with methylscopolamine, diminished after atropine and totally **inhibited** after hexamethonium. In addition, activation of **muscarinic** receptors in the pontine-mesencephalic brain region with oxotremorine after methylscopolamine pretreatment generates a hyperactive **urinary bladder** response, mediation of which seems to be independent of endogenous catecholamine stores. It is suggested that cholinergic receptors in the pontine-mesencephalic brain region are of importance for regulation of **urinary bladder** function in the rat. Furthermore, the **bladder** hyperactivity induced by L-DOPA might be propagated via **muscarinic** receptors in this brain area, and mediated peripherally via cholinergic receptors in the autonomic ganglia, but in the **bladder** detrusor via non-cholinergic receptors.

L12 ANSWER 107 OF 121 MEDLINE on STN
ACCESSION NUMBER: 83091092 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6129625
TITLE: Direct evidence against a role of ATP as the nonadrenergic, noncholinergic **inhibitory** neurotransmitter in guinea pig tenia coli.
AUTHOR: Westfall D P; Hogaboom G K; Colby J; O'Donnell J P; Fedan J S
CONTRACT NUMBER: S T32 GM07039 (NIGMS)
NB08300
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1982 Nov) 79 (22) 7041-5.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198302
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19970203
Entered Medline: 19830225

AB Electrical field stimulation of the isolated guinea pig tenia coli in the presence of a **muscarinic** receptor antagonist (atropine) and an adrenergic neuron blocker (guanethidine) produces relaxation. A large amount of indirect evidence has suggested that the neurotransmitter that is released from these nonadrenergic, noncholinergic **inhibitory** neurons is ATP or a related nucleotide, and the nerves have been termed "purinergic." A photoaffinity analog of ATP, arylazido aminopropionyl ATP, which produces a specific pharmacological antagonism of P2 purinergic receptors in isolated guinea pig vas deferens and **urinary bladder**, was utilized in the present study to evaluate directly whether ATP is the nonadrenergic, noncholinergic **inhibitory** neurotransmitter in tenia coli. By blocking postjunctional P2 receptors, arylazido aminopropionyl ATP produced a pronounced antagonism of relaxations induced by exogenously added ATP. Responses produced by ADP, AMP, and adenosine also were antagonized by arylazido aminopropionyl ATP, but to a lesser extent. **Inhibitory** responses to isoproterenol were not antagonized. Under these conditions of established, specific P2-receptor blockade of responses to exogenously added ATP, relaxations induced by field stimulation of intrinsic **inhibitory** nerves in the presence of atropine (1 microM) and guanethidine (1 microM) were not antagonized. Though these results provide no indication of the actual substance involved, they suggest strongly that the nonadrenergic, noncholinergic **inhibitory** neurotransmitter in the guinea pig tenia coli is not ATP.

L12 ANSWER 108 OF 121 MEDLINE on STN
ACCESSION NUMBER: 82196037 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6281697
TITLE: Effect on neuromuscular transmission of repeated administration of an organophosphorus compound, metrifonate, during treatment of children with **urinary** schistosomiasis.
AUTHOR: Maxwell I C; Le Quesne P M; Ekue J M; Biles J E
SOURCE: Neurotoxicology, (1981 Dec) 2 (4) 687-701.
Journal code: 7905589. ISSN: 0161-813X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198207
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19820708

AB Muscle action potential amplitude recorded from abductor pollicis brevis in response to nerve stimulation was measured in 55 children during treatment of **urinary** schistosomiasis with metrifonate (3 doses at 2 weekly intervals). Mean erythrocyte **cholinesterase** activity was 52-75% of pretreatment value in different groups when examined electrophysiologically. Twenty-six children acted as controls. There was no difference in amplitude between control and exposed subjects 2 weeks after the 2nd dose. Six hours after the 3rd dose, amplitude was larger in some subjects. This effect was not related to dose or degree of **cholinesterase inhibition** and was thought unlikely to be the result of treatment. Three children who received the highest dose of metrifonate had developed repetitive activity 6 hr later. The criteria for its identification are described.

L12 ANSWER 109 OF 121 MEDLINE on STN
ACCESSION NUMBER: 81200946 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6112793
TITLE: Central neurotransmitter mechanisms involved in the control of **urinary bladder** function. An experimental study in the rat.
AUTHOR: Sillen U
SOURCE: Scandinavian journal of urology and nephrology. Supplementum, (1980) 58 1-45.
Journal code: 0153034. ISSN: 0300-8886.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198107
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19980206
Entered Medline: 19810720

AB Central neurotransmitter systems have been activated in anaesthetized rats, while the effects on the **urinary bladder** have been recorded by cystometric procedures. Stimulation of central catecholamine neurons with the amine precursor L-3,4 dihydroxyphenylalanine (L-DOPA), after peripheral **inhibition** of the degradating enzyme dopadecarboxylase, resulted in a hyperactive **urinary bladder** response. This **bladder** action seems to be elicited mainly via central dopamine receptors, and mediated via neurons of non-catecholamine type. Activation of central **muscarinic** receptors with oxotremorine, after pretreatment with methylscopolamine, induced a hyperactive **urinary bladder** response, which is suggested to originate in pontine-mesencephalic structures as well. There might in some instances be an interaction with **muscarinic** receptors in the generation of the **bladder** hyperreactivity to L-DOPA, at the pontine-mesencephalic brain level. The **bladder** response to stimulation of central **muscarinic** receptors, on the other hand, seems to be independent of intact adrenergic neurons. The peripheral mediation of the **bladder** response to L-DOPA is propagated via the pelvic nerves; in the peripheral ganglia via cholinergic receptors, but in the **bladder** detrusor via non-cholinergic as well as non-adrenergic receptors. Activation of central GABA mechanisms with GABA, muscimol and diazepam strongly **inhibited** the **bladder** hyperactivity to L-DOPA. This **inhibition** probably occurred in the pontine-mesencephalic brain area. The results suggest that excitatory dopaminergic and **muscarinic** receptors, as well as **inhibitory** gabaergic receptors in the pontine-mesencephalic brain region, are involved in the modulation of the **urinary bladder** function.

L12 ANSWER 110 OF 121 MEDLINE on STN
ACCESSION NUMBER: 81109764 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7193020
TITLE: Pharmacology of secoverine, a new spasmolytic agent with specific antimuscarinic properties. Part 1: Antimuscarinic and spasmolytic effects.
AUTHOR: Zwagemakers J M; Claassen V
SOURCE: Arzneimittel-Forschung, (1980) 30 (9) 1517-26.
Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198103
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810317

AB 1-Cyclohexyl-4-[ethyl(p-methoxy-alpha methylphenethyl)amino]-1-butanone hydrochloride (secoverine hydrochloride) is a neurotropic spasmolytic agent with specific antimuscarinic properties. On the basis of the results obtained, the possibility exists that secoverine acts only a sub-group of **muscarinic** receptors. 1. In in vitro experiments the competitive antagonism of secoverine against muscarinomimetics was demonstrated on guinea pig ileum, rat jejunum and calif trachea smooth muscle. On the basis of the mean difference of the pA2 values and in accordance with the relative activity as determined by 4-point assays, it may be concluded that secoverine is about 0.6 times as active as atropine. 2. In in vivo experiments the antimuscarinic activity of secoverine on ileum of guinea pig, rat and dog proved to be 0.6 times of atropine, by both parenteral and intraduodenal routes of administration. It was shown that the action of secoverine was reversible, of quick onset and of long duration. 3. By contrast, secoverine had only marginal effects on the sphincter and ciliary muscle of the eye, almost no effect on cholinergically-induced salivation and lacrimation, gastric acid production, **urinary bladder** function, gastric emptying or normal peristalsis. 4. The central anticholinergic activity was more in accordance with the activity found in the spasmolytic tests. 5. Apart from the neurotropic action, secoverine has also a good musculotropic activity as was found in in vivo and in vitro experiments. The activity varied from 3.3--13.3 times that of papaverine in the different organs investigated. The musculotropic activity is not caused by a specific, verapamil-like, calcium antagonism. 6. Secoverine has no nicotinolytic or antihistaminic activity, a moderate antisterotonic activity, an **inhibiting** effect on the noradrenaline uptake mechanism of the vas deferens and a marked local anaesthetic activity.

L12 ANSWER 111 OF 121 MEDLINE on STN
ACCESSION NUMBER: 81090827 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7449999
TITLE: [Possibility of substance selective action on the m-cholinoreceptors of a specific site]. O vozmozhnosti izbiratel'nogo deistviia veshchestv na m-kholinoretseptory opredelennoi lokalizatsii.
AUTHOR: Kharkevich D A; Skoldinov A P; Samailov D N; Shorr V A
SOURCE: Farmakologiia i toksikologiia, (1980 Nov-Dec) 43 (6) 645-52.
Journal code: 16920420R. ISSN: 0014-8318.
PUB. COUNTRY: USSR
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198103
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19970203
Entered Medline: 19810327

AB Effects of a number of agents on the muscarine-sensitive acetylcholine receptors (**muscarinic** receptors) of different localization were investigated. Experiments on anesthetized cats revealed the following effects of acetylcholine: hypotension, bradycardia, bronchospasm, contractions of the ileum and **urinary bladder**, hypersalivation. It was shown that the highest sensitivity to bisquaternary ammonium derivatives of diphenyl cyclobutanedicarboxylic (truxillic) acid is exhibited by the **muscarinic** receptors of the heart. The sensitivity of bronchial **muscarinic** receptors is slightly lower. The prevailing action on the **muscarinic** receptors of the heart was also shown by some N-adamantyl bisquaternary ammonium compounds. Procaine and the antihistaminics mebhydroline and diphenhydramine eliminated bradycardia induced by acetylcholine without affecting the latter's hypotensive effect. The evidence obtained indicates the heterogeneity of the **muscarinic** receptors of different localization.

L12 ANSWER 112 OF 121 MEDLINE on STN
ACCESSION NUMBER: 81024354 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6106562
TITLE: **Inhibition** and facilitation in parasympathetic ganglia of the **urinary bladder.**
AUTHOR: de Groat W C; Booth A M
CONTRACT NUMBER: NS 07923 (NINDS)
SOURCE: Federation proceedings, (1980 Oct) 39 (12) 2990-6. Ref: 37
Journal code: 0372771. ISSN: 0014-9446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198012
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19970203
Entered Medline: 19801216

AB Neurons in vesical parasympathetic ganglia receive excitatory and **inhibitory** inputs from both divisions of the autonomic nervous system. Sacral parasympathetic pathways (cholinergic) provide the major excitatory input to these ganglia via activation of nicotinic receptors. Parasympathetic pathways also activate **muscarinic inhibitory** and excitatory receptors, which may exert a modulatory influence on transmission. Cholinergic transmission is relatively inefficient when preganglionic nerves are stimulated at low frequencies (< 1 Hz). However, excitatory postsynaptic potentials (EPSPs) and postganglionic firing markedly increase during repetitive stimulation at frequencies of 1-10 Hz. It is concluded that enhanced transmitter release accounts for the temporal facilitation and that vesical ganglia function as "high pass filters" that amplify the parasympathetic excitatory input to the detrusor muscle during micturition. Transmission in vesical ganglia is also sensitive to adrenergic **inhibitory** and facilitatory synaptic mechanisms elicited by efferent pathways in the hypogastric nerves. The effects of exogenous norepinephrine indicate that adrenergic **inhibition** is mediated by alpha receptors and reflects primarily a presynaptic depression of transmitter release although postsynaptic adrenergic hyperpolarizing and depolarizing effects have also been noted. Adrenergic facilitation is mediated by beta receptors as well as unidentified receptors. Norepinephrine also can **inhibit** or excite spontaneously active neurons in vesical ganglia. The existence of **inhibitory** and facilitatory synaptic mechanisms in vesical ganglia provides the basis for a complex ganglionic modulation of the central autonomic outflow to the **bladder.**

L12 ANSWER 113 OF 121 MEDLINE on STN
ACCESSION NUMBER: 80252482 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6249955
TITLE: Cholinergic **inhibition** of **urinary** acidification by the turtle **bladder.**
AUTHOR: Arruda J A; Sabatini S
SOURCE: Kidney international, (1980 May) 17 (5) 622-30.
Journal code: 0323470. ISSN: 0085-2538.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198010
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19801024

AB The effect of carbachol on **urinary** acidification by the turtle **bladder** in vitro was studied. Carbachol **inhibited urinary** acidification in a dose dependent fashion, with half maximal **inhibition** occurring at 4.5 x 10(-5) M. The effect of carbachol on **urinary** acidification could be totally prevented by atropine, indicating that the **inhibition** is mediated through a **muscarinic** receptor. Carbachol **inhibited** hydrogen ion secretion by decreasing the active proton conductance and not by altering the proton motive force. Carbachol failed to increase passive loss of hydrogen ion from the mucosa. Carbachol increased calcium uptake by the turtle **bladder**; this increase in calcium uptake could be prevented by pretreatment with atropine, pentobarbital, or lanthanum. Pentobarbital or lanthanum blunted the **inhibitory** effect of carbachol on hydrogen ion secretion. In the presence of low extracellular calcium (0.2 mM), carbachol failed to increase calcium uptake but caused a significant **inhibition** of hydrogen ion secretion. In the presence of normal calcium concentration, carbachol caused a significant efflux of calcium. These data demonstrate that carbachol **inhibits urinary** acidification and suggest that the mechanism of this **inhibition** may be related, at least in part, to changes in cytosolic calcium.

L12 ANSWER 114 OF 121 MEDLINE on STN
ACCESSION NUMBER: 79021892 MEDLINE
DOCUMENT NUMBER: PubMed ID: 81076
TITLE: [Effect of acetylcholine on the pituitrin induced osmotic flow of water through the wall of the frog **urinary bladder**]. Vliianie atsetilkholina na vyzvannyi pituitrinom osmoticheskii tok vody cherez stenku mochevogo puzyria liagushki.
AUTHOR: Bagrov Ia Iu; Manusova N B
SOURCE: Biulleten' eksperimental'noi biologii i meditsiny, (1978 Sep) 86 (9) 321-4.
Journal code: 0370627. ISSN: 0365 9615.
PUB. COUNTRY: USSR
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197812
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19781227

AB The role of intercellular pathways in the ADH dependent water transport was studied on the frog **urinary bladder** by means of acetylcholine (AC) and other cholinergic compounds. AC (10(-3) M) was found to cause a strong suppression of the pituitrin-stimulated water flow. Analogous effect was produced by AC on the osmotic flow stimulated by cyclic adenosine monophosphate (cAMP) and theolin. The antipituitrin effect was not reproduced either by nicotine, nor by potent M-cholinomimetic agents (methylfurmetide and F-2268), and was not prevented by M- and N-cholynolytic drugs (atropine, metacin, flaxedil, hexamethonium). However, the antipituitrin effect of AC was completely removed by the anticholinesterase drugs with different mode of action (eserine, proserine, armin, acridine iodmethylate, GD-42) in concentrations of 10(-6)--10(-3) M. It was concluded that the smooth muscles contraction with the subsequent closure of the intercellular spaces was not responsible for the antipituitrinic action of AC. This effect appears to be connected with **cholinesterase** activation. A possible role of the phosphoinositides in the water permeability regulation of the **urinary bladder** wall is discussed.

L12 ANSWER 115 OF 121 MEDLINE on STN
ACCESSION NUMBER: 77217117 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17940
TITLE: Uropharmacology: v. choline esters and other parasympathomimetic drugs.
AUTHOR: Finkbeiner A E; Bissada N K; Welch L T
SOURCE: Urology, (1977 Jul) 10 (1) 83-9. Ref: 51
Journal code: 0366151. ISSN: 0090-4295.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197708
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19950206
Entered Medline: 19770825

AB Various parasympathomimetic drugs are discussed, including the choline esters, bethanechol, carbachol, methacholine chloride, and furtrethonium. Other cholinomimetic agents include muscarine, muscarone, arecholine, and pilocarpine. Anticholinesterase agents **inhibit** or inactivate acetylcholinesterase enzyme and thus result in a prolonged stimulation of cholinergic receptors by endogenous ACh. Bethanechol is the most widely used parasympathomimetic drug in the United States. Its action is mainly **muscarinic** with activity largely confined to the **urinary bladder** and to a lesser degree the gastrointestinal tract. It can be administered only subcutaneously or orally, and adequate dosage is necessary for a successful response.

L12 ANSWER 116 OF 121 MEDLINE on STN
ACCESSION NUMBER: 77194773 MEDLINE
DOCUMENT NUMBER: PubMed ID: 866699
TITLE: The role of prostaglandins in the excitatory innervation of the rat **urinary bladder.**
AUTHOR: Choo L K; Mitchelson F
SOURCE: Prostaglandins, (1977 May) 13 (5) 917-26.
Journal code: 0320271. ISSN: 0090-6980.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197707
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19770729

AB The possible role of PGs in hyoscine-resistant nerve mediated responses of the rat **urinary bladder** was investigated. Responses to electrical stimulation were **inhibited** by cinchocaine (30 micronmol/1) but were only partially **inhibited** by a high concentration of hyoscine (25 micronmol/1) or by the choline uptake **inhibitors**, hemicholinium-3 (500 micronmol/1) and troxypyrrolidinium (500 micronmol/1). Indomethacin (50 micronmol/1) produced partial blockade (30%) of responses to electrical stimulation without markedly affecting responses to acetylcholine and the degree of blockade was of a similar order in the presence of hyoscine or troxypyrrolidinium. PGE2 (0.028 -2.8 micronmol/1) or F2alpha (0.029 -2.9 micronmol/1) produced a slowly developing increase in tone and spontaneous activity. Responses to electrical stimulation were at most only slightly increased in the presence of either PG. However, the PGs always increased the responses to electrical stimulation after indomethacin, indomethacin plus hyoscine or indomethacin plus troxypyrrolidinium. Responses to acetylcholine in the presence of indomethacin were not increased by PGE2. It is concluded that PGE2 and F2alpha do not function is transmitters responsible for resistance to anti-**muscarinic** drugs in the **bladder** but may exert a modulating effect on nervous transmission.

L12 ANSWER 117 OF 121 MEDLINE on STN
ACCESSION NUMBER: 77113136 MEDLINE
DOCUMENT NUMBER: PubMed ID: 837006
TITLE: Atropine resistance and **muscarinic** receptors in the rat **urinary bladder.**
AUTHOR: Carpenter F G
SOURCE: British journal of pharmacology, (1977 Jan) 59 (1) 43-9.
Journal code: 7502536. ISSN: 0007 1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197704
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19770425

AB The action of an anticholinesterase and an antimuscarinic drug upon nerve-induced contractions of the rat **urinary bladder** were examined during transmural stimulation at 20 Hz. Responses were graded in magnitude by limiting the duration of the stimulus trains. 2 Responses of low magnitude produced by short stimulus trains were unchanged by atropine; however, maximal responses resulting from long stimulus trains were diminished in magnitude and shortened in duration. 3 Responses of small magnitude elicited by short stimulus trains involve **muscarinic** receptors in close proximity to the neuroeffector junction and are resistant to atropine. 4 Maximal responses elicited by long stimulus trains involve 'junctional' **muscarinic** receptors as well as receptors located at the periphery of the junction; the 'extrajunctional' receptors are blocked by atropine. 5 Responses of low magnitude produced by short stimulus trains were unaffected by echothiophate; however, the duration of maximal responses resulting from the long stimulus trains was extended. 6 The **inhibition** of **cholinesterase** did not increase the occupation of **muscarinic** receptors by the transmitter; however, after large quantities of transmitter were released by the long stimulus trains the association between the receptors and acetylcholine was prolonged.

L12 ANSWER 118 OF 121 MEDLINE on STN
ACCESSION NUMBER: 74261431 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4838789
TITLE: [Combination of various therapeutic methods in the therapy of insufficient closure of the **bladder** in old women].
Beitrag zur Kombination mehrerer Behandlungsverfahren des insuffizienten Blasenverschlusses bei alten Frauen.
AUTHOR: Slunsky R
SOURCE: Zentralblatt fur Gynakologie, (1974 Feb 22) 96 (8) 225-30.
Journal code: 21820100R. ISSN: 0044-4197.
PUB. COUNTRY: GERMANY, EAST: German Democratic Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197408
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19740828

L12 ANSWER 119 OF 121 MEDLINE on STN
ACCESSION NUMBER: 74147575 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4823891
TITLE: The effect of Ubretid on **bladder** function after recent complete spinal cord injury.
AUTHOR: Smith P H; Cook J B; Prasad E W
SOURCE: British journal of urology, (1974 Apr) 46 (2) 187 92.
Journal code: 15740090R. ISSN: 0007-1331.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197406
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19740619

L12 ANSWER 120 OF 121 MEDLINE on STN
ACCESSION NUMBER: 72050602 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4941704
TITLE: [Therapy of **bladder** sphincter incontinence in females].
Therapie der Inkontinenz des Sphinkter vesicae bei der Frau.
AUTHOR: Palmrich A H
SOURCE: Medizinische Klinik, (1971 Oct 15) 66 (42) 1405 9. Ref: 38
Journal code: 0376637. ISSN: 0025-8458.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197202
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19720202

L12 ANSWER 121 OF 121 MEDLINE on STN
ACCESSION NUMBER: 72010885 MEDLINE
DOCUMENT NUMBER: PubMed ID: 5520362
TITLE: Differentiation of receptors for exogenous and endogenous acetylcholine in the **urinary bladder**.
AUTHOR: Chesher G B
SOURCE: Agents and actions, (1970 Mar) 1 (3) 128-32.
Journal code: 0213341. ISSN: 0065-4299.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197112
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19711209